Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio as Prognostic Markers of Systemic Lupus Erythematosus Activity

Thesis

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Ahmed Mamdouh
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List of abbreviations

AAP	Acute abdominal pain
ACR	American College of Rheumatology
ANA	antinuclear antibodies
Anti-dsDNA	anti-double-stranded DNA
BILAG	British Isles Lupus Assessment Group
C3	Complement 3
C4	Complement 4
CBC	Complete blood count
CNS	Central Nervous System
CRC	colorectal cancer
CRP	C-reactive protein
CVD	Cardio Vascular Disease
DNA	deoxyribonucleic acid
eGFR	estimated glomerular filtration rate
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GI	gastrointestinal
HCC	Hepato Cellular Carcinoma
HF	Heart Failure
HRQOL	health-related quality of life
IL	interleukin
LDL	low-density lipoprotein

LFTs	liver function tests
LUMINA	Lupus in Minorities: Nature versus Nurture
MPV	Mean Platelet Volume
NLR	Neutrophil-lymphocyte ratio
NPSLE	neuropsychiatric SLE
NSAIDS	Nonsteroidal anti-inflammatory drugs
OS	Overall Survival rate
PGA	Physician Global Assessment
PLR	Platelet to lymphocyte ratio
RA	Rheumatoid Arthritis
SCORAD	SCORing Atopic Dermatitis
SFI	SELENA-SLEDAI Flare Index
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
TAK	Takayasu's arteritis
US	United States
WBC	White blood cell
WHO	World Health Organization

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Introduction:

Systemic Lupus Erythematosus is a chronic multi- organ autoimmune disease in which the body's immune system mistakenly attacks healthy tissue in many parts of the body. Symptoms vary between people and may be mild to severe. Common symptoms include painful and swollen joints, fever, chest pain, hair loss, mouth ulcers, enlarged lymph nodes, fatigue ***(Wu et al., 2016)***

The global rates of SLE are approximately 20-70 per 100,000 people. In females, the rate is highest between 16-45 year of age. The lowest overall rate exists in Iceland and Japan. The highest rates exist in US and France. SLE, like many autoimmune diseases, affects females more frequently than males, at a rate of about 9 to 1***(Danchenko et al., 2006)***

Most patients with SLE develop kidney disease related to this systemic underlying disease process. Lupus nephritis is the most common and severe clinical manifestation of SLE ***(Borchers et al., 2012)***

White blood cell (WBC) count is a serum marker for systemic Inflammation. Neutrophil-lymphocyte ratio is easily calculated by dividing neutrophil

count by the absolute lymphocyte count from a complete blood count. It is simple and cheap. Many studies have shown that NLR is positively associated with inflammatory, different malignancies, ischemic injury, cardiovascular disease and diabetic nephropathy . Also , Pericarditis and pericardial effusions in SLE are well recognized in SLE ***(Ahsen et al., 2013) (Li et al., 2014) (Maharaj et al., 2015)***

Platelet to lymphocyte ratio (PLR) is an easy calculated parameter. Studies have shown that increased PRL is associated with neoplastic diseases like lung cancer .Moreover PLR is a better predictor than NLR for survival in patients with ovarian cancer***.(Feng et al., 2013)***

The most commonly used parameters of lupus is called the SLE Disease Activity Index, and the acronym for it is SLEDAI. The SLEDAI index is a global score index developed for the assessment of SLE disease activity depending on many signs , laboratory investigations and other criteria of the disease ***(Bombardier et al., 1992)***

Understanding SLE

Definition:

Systemic Lupus Erythematous (SLE) is a chronic multi organ autoimmune disease in which the body immune system mistakenly attacks healthy tissue in many parts of the body. Symptoms vary between patients and may be mild to severe. Common symptoms include painful and swollen joints, fever, chest pain, loss, mouth ulcers, enlarged lymph nodes and fatigue ***(Wu et al., 2016)***

The global rates of SLE are reported as 20-70 per 100,000 people. In females, the rate is highest between 16- 45 year of age. The lowest overall rate exists in Iceland and Japan. The highest rates exist in US and France. SLE, like many autoimmune diseases, affects females more frequently than males ,at a rate of about 9 to 1***.(Danchenko et al., 2006)***

Genetic Consideration

Concordance rates for SLE among monozygotic and dizygot twins are 25% and 2% respectively, suggesting a significant genetic contribution (***Gaubitz ; 2006***)

Pathogenesis of SLE

SLE is a complex disease process demonstrating dysregulation of the immune system at multiple levels .Autoantibodies against double-stranded DNA were first isolated from kidney specimens in patients with lupus nephritis in 1967***(Simard and Costenbader,2007)***

One manifestation of SLE is abnormalities in apoptosis, a type of Programmed cell death in which aging or damaged cells are disposed of as a part of normal growth or functioning. In SLE, the body's immune system produces antibodies against itself, particularly against proteins in the cell nucleus. SLE is triggered by environmental factors that are unknown. The immune system must balance between being sensitive enough to protect against infection, and become sensitized to attack the body's own proteins (autoimmunity). During an immune reaction to a foreign stimulus , such as bacteria, virus, or allergen, immune cells that would normally be deactivated due to their affinity for self-tissues can be abnormally activated by signaling sequences of antigen-presenting cells. Thus triggers may include viruses, bacteria, allergens (IgE and other hypersensitivity), and can be aggravated by environmental stimulants such as ultraviolet light and

certain drug reactions. These stimuli begin a reaction that leads to destruction of other cells in the body and exposure of their DNA, histones, and other proteins, particularly parts of the cell nucleus. The body's sensitized B-lymphocyte cells will now produce antibodies against these nuclear-related proteins. These antibodies clump into antibody-protein complexes which stick to surfaces and damage blood vessels in critical areas of the body, such as the glomeruli of the kidney; these antibody attacks are the cause of SLE . Researchers are now identifying the individual genes, the proteins they produce, and their role in the immune system. Each protein is a link on the autoimmune chain , and researchers are trying to find drugs to break each of those links. (***Mary;2008)***

Two major theories exist on how these auto-antibodies cause tissue damage. The first model suggests that anti-double-stranded DNA antibodies bind to circulating nucleosomes to form immune complexes that then get deposited in end-organ capillary beds such as the renal glomerulus and activate immune/inflammatory responses**.*(Sestak et al ., 2005)***

The second hypothesizes that these auto-antibodies cross-react with normal renal proteins causing tissue destruction ***(Moser et al., 2009)***

Medications, hormonal influences, and other factors such as sunlight have all been implicated in disease exacerbation. Drug-Induced lupus, most commonly due to procainamide, hydralazine, and quinidine, usually presents with disease involving the skin and joints with renal and CNS manifestations being much more rare ***(Costenbader et al.,2004)***

Clinical Features

A variety of disease manifestations are exhibited by SLE patients ,with the heterogenity of presentations often delaying diagnosis. Common manifestations include rashes, photosensitivity, arthritis, pleuritis, pericarditis, nephritis, neuropsychiatric disorders, and hematological disorders. There is also an array of less common but potentially hazardous complications.

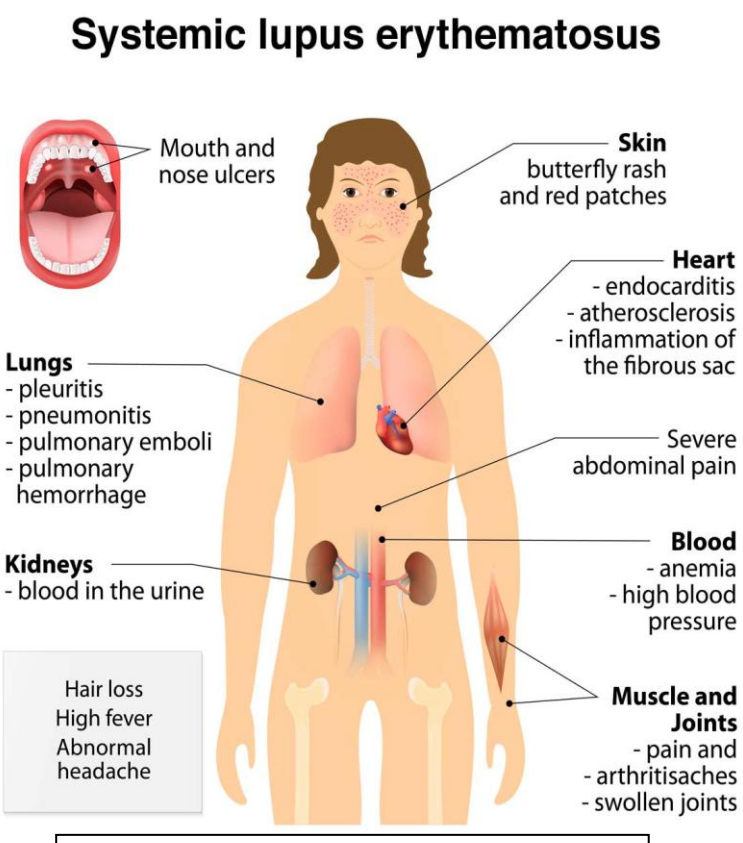

Fig (1): Clinical features of SLE (***Rullo and Tsao,2013)***

A.Cardiovascular:

Pericarditis is well recognized in lupus and is included as a diagnosing criterion by the ACR .One-quarter of lupus patients develop symptomatic pericarditis, while >50% have evidence of asymptomatic pericardial involvement **.** ***(Moder et al.,1999)***.

Nonsteroidal anti-inflammatory drugs (NSAIDS) and corticosteroids are standard management, but pericardiocentesis or pericardial window procedures may be required for treatment of tamponade. Myocarditis is characteristic of myocardial involvement in SLE, with 5%–10% of patients experiencing clinically evident disease**,** and up to 80% of these have decreased left ventricular ejection fraction ***(Law et al ., 2007).***

The pathological process is probably immunological with immune complexes and complement deposition evident in perivascular myocardium. SLE myocarditis can progress to arrhythmias, ventricular dysfunction, dilated cardiomyopathy and heart failure, although other factors may be responsible such as hypertension, accelerated atherosclerosis with ischemia, valvular disease, renal failure, and treatment toxicity from cyclophosphamide or hydroxychloroquine. ***(Urowitz et al .,2011)***

The impact of cardiovascular disease as a cause for late complications has been confirmed. Epidemiological studies highlight the significant risk in some populations women ages 44 to 50 years with SLE had a 50-times increased likelihood of myocardial infarction when compared with controls from the Framingham study **.**SLE is clearly an independent risk factor for the development of CVD, and as a result, traditional risk factor models perform less well in this population ***(Ahmad et al., 2007)***

Thus, the clinician must have a lower threshold for suspicion of CVD in these patients, despite the absence of classical risk factors. Cohort studies identified specific risk factors associated with development of CVD in SLE patients, including older age at diagnosis of SLE, longer disease duration, duration of steroid use, and hypercholesterolemia***. (Petri et al .,1992)***.

The overlapping inflammatory and immune-mediated nature of both SLE and atherosclerosis is being increasingly recognized, and is seen as part of the functional cause of the premature CVD noted in lupus patients. Activated immune-mediating cells are typical of atherosclerotic plaques and elevated C-reactive protein has been associated with CVD risk in the general population

and more specifically in SLE patients as well. SLE patients develop a typical dyslipidemia characterized by increased low-density lipoprotein (LDL), increased triglycerides, and reduced high-density lipoprotein which is aggravated by flares ***(De Carvalho et al., 2008)***

Clinically significant valvular dysfunction occurs in 3%–4% of SLE patients, with about half requiring surgery. Rhythm and conduction abnormalities are noted in SLE patients, most commonly sinus tachycardia , atrial fibrillation, and atrioventricular block ***(Seferovic et al., 2006)***

B.Pulmonary:

Lupus can affect all pulmonary tissues, and abnormalities are common among lupus patients. Significant lung pathology was found in 18% of patients in one autopsy study **,** and two thirds of patients had subclinical defects on lung function testing, most commonly a deficit in the diffusing capacity of carbon monoxide. Radiological changes often seen with high-resolution computed tomography include the following: ground-glass and reticular opacities; features of interstitial lung disease present in one third; airway abnormalities

noted in one fifth of asymptomatic patients; and frequent mediastinal lymphadenopathy .Pleural disease is the most likely clinical manifestation of SLE ,with up to 35% of patients presenting with pleuritis. Pleural effusions when present are usually only mild, but large and clinically relevant effusions may develop***. (Fenlon et al ., 1996 ; Swigris et al ., 2008)***

Parenchymal manifestations include interstitial lung disease, diffuse alveolar hemorrhage, and acute lupus pneumonitis. High-resolution computed tomography provides diagnostic support to clinical suspicion, while tissue sampling commonly reveals cellular, fibrotic, or mixed nonspecific interstitial pneumonia***.(Tansey et al., 2004).***

Diffuse alveolar hemorrhage is a potentially severe complication occurring in 1%–5% of SLE patients and carrying a 50% mortality. It should be suspected in any case of new dyspnea, ground- glass opacities, or decreasing hematocrit with or without hemoptysis, with diagnosis being confirmed on bronchoalveolar lavage. Patients often require supportive intensive care, aggressive immunosuppression, and plasmapheresis with or without mechanical ventilation. Pulmonary arterial hypertension is an uncommon but

well-documented complication of SLE, with a reported prevalence of 0.5%–14%. Diagnosis is often delayed because usual symptoms of dyspnea, fatigue, and impaired exercise tolerance are nonspecific. Several processes contribute to development of pulmonary arterial hypertension, including thromboembolism, pulmonary vasculitis, and fibrosis secondary to interstitial lung disease; treatment involves a combination of immunosuppression and standard therapies***. (Pope , 2008)***

C.Laryngeal Involvment:

Laryngeal complications in SLE have been recognized for 50 years, with an incidence ranging from 0.3% to 30%. Findings include mild inflammation, vocal cord paralysis, subglottic stenosis, and laryngeal edema with acute obstruction. Most cases arise in patients with pre- existing SLE, although laryngeal manifestations may rarely be the presenting feature. There exist case reports of vocal cord paralysis, and an association with pulmonary hypertension has been found, presumably due to right atrial/pulmonary artery enlargement causing compression of the recurrent laryngeal nerve ***(Diane and Charlie, 2010)***

Epiglottitis, rheumatoid type nodules, inflammatory masses, and cricoarytenoiditis have been described as well. Most cases respond to immunosuppressive therapy, although emergent endotracheal intubation or surgical tracheostomy has rarely been required. There is also some suggestion that active SLE may also predispose to post-intubation subglottic stenosis even after relatively brief periods of tracheal intubation***.(Raj et al ., 2002)***

D.Renal:

Lupus nephritis is common and carries a high burden of morbidity in SLE patients, both directly and as a result of treatment complications. Clinically relevant nephritis develops in 60% of patients, often within the first 3 years of lupus diagnosis. ***(Singh and Saxena , 2009)***

One third of SLE patients present with lupus nephritis within the first year of diagnosis. Renal complications have a standardized mortality ratio estimated at 4.3 and also independently predict mortality in damage accrual indexes. ***(Danila et al., 2009)***

The pathogenesis of lupus nephritis is complex but may reflect either the deposition of circulating immune complexes, such as anti-dsDNA, into the

glomerulus and subsequent activation of complement, or a direct pathogenic mechanism whereby autoantibodies react with proteins in the kidney such as actinin. Additional mechanisms of damage are being recognized, including renal vasculitis, thrombotic microangiopathy, injury to podocytes, and dysregulation of inflammatory mediators.***(Schwartz ,2007)***

Proteinuria is the hallmark of renal disease in lupus and is extremely common, though hematuria is less common. Urinary casts are often seen, reflecting renal tubular dysfunction, and hyperkalemic renal tubular acidosis has been associated with lupus. About 5%–20% of nephritic patients will progress to end -stage renal disease although rates appear to be decreasing and survival improving as a result of improved treatment regimens. Kidney biopsy is the "gold standard" for the diagnosis and classification of lupus nephritis. The 2004 revision of the (WHO) World Health Organization system by the International Society of Nephrology identifies 6 categories based on histological findings.***(Weening et al ., 2004)***

Focal proliferative (Class III) and diffuse proliferative (Class IV) disease have a poor prognosis for renal survival and are associated with severe

hypertension. Two thirds of Class III patients progress to Class IV, and it is widely accepted that Class IV lupus nephritis carries the worst prognosis**.** ***(Najafi et al ., 2001)***

Biopsy is indicated in patients with evidence of underlying pathology such as increased creatinine, proteinuria, hematuria, or abnormal urinary sediments, but it is increasingly recognized that even in the absence of such findings, patients may have significant pathology on biopsy. One retrospective review found no correlation between serum creatinine or proteinuria and biopsy findings, and a large proportion of patients with normal renal function were found to have Class IV diffuse proliferative lupus nephritis on biopsy. It would therefore be appropriate to take precautions for renal protection in lupus patients even in the presence of normal serum creatinine and urinary analysis**.** ***(Jacobsen et al ., 1999)***

E.Neurological:

SLE causes central nervous system (CNS), peripheral nervous system, autonomic nervous system, and psychiatric complications and is reported to affect between 37% to 95% of patients***.(Hanly , 2005)***

The ACR recommends the term neuropsychiatric SLE (NPSLE) to encompass all possible manifestations. Nineteen separate categories were created, classifying manifestations on the basis of pathological location, but inclusion of some categories remains controversial. When neurological symptoms arise, it is essential to consider differential diagnoses that may coexist. There is controversy because much of the healthy population exhibits at least 1 manifestation listed in the ACR definition for NPSLE. Aniala et al. studied 46 SLE patients and 46 controls and found at least 1 NPSLE manifestation in 91% and 54% of patients and controls , respectively, but after the exclusion of the most common manifestations (headache, anxiety, mild depression, mild cognitive impairment, and polyneuropathy without electrophysiological confirmation), the prevalence of NPSLE decreased to 54% and 7%, respectively***.(Aniala et al ., 2001)***

Headaches have been reported in 50% of SLE patients, often of the migraine or tension type, but a 2004 meta- analysis failed to confirm an association between SLE and headaches **.**Seizures are reported by 7%–20% of patients and may be the result of direct antibody activity against neural elements. Seizures secondary to SLE represent a diagnosis of exclusion and require full investigation for alternate causes. ***(Greenberg , 2009)***

Psychosis, movement disorders, acute confusional states, and demyelinating disease are also reported. Transverse myelitis or a demyelinating process resembling multiple sclerosis can complicate SLE. SLE myelitis presents with spinal cord injury with paralysis, sensory deficits, and smooth muscle dysfunction. Additionally, several studies show higher rates of dysautonomia in SLE patients**.*(Stojanovich et al ., 2007)***

F. Hematological:

Hematological derangements in SLE are widely recognized, with lymphopenia being the most common, although anemia and thrombocytopenia are also seen. Anemia is found in about half of SLE patients with the most common cause being anemia of chronic disease;

however, other causes include autoimmune hemolytic anemia, iron deficiency anemia, anemia of chronic renal failure and cyclophosphamide myelotoxicity. Autoimmune hemolytic anemia occurs in about 5%–10% of SLE patients, although positive Coombs' tests without actual hemolysis are found in a much higher proportion. Antierythrocyte antibodies are implicated in the pathogenesis of autoimmune hemolytic anemia, and there is also a strong correlation between Anticardiolipin antibodies and Coombs'positive hemolytic anemia which may contribute to the pathogenesis of cytopenia rather than simply being induced as a result of cellular breakdown. This would explain combined anemia/ thrombocytopenia better than specific antibodies to respective cell types. Most cases of anemia are mild, but severe cases with hemoglobin below 8.0 g/dL do occur, often coexisting with significant renal or CNS disease. ***(Giannouli et al .,2007)***

Thrombocytopenia occurs either in isolation or as part of a broader hematological disturbance. The prevalence of autoimmune thrombocytopenia has been reported as 9.5% of SLE patients, and its occurrence may precede the diagnosis of SLE, with 3%–16% of idiopathic thrombocytopenic patients

eventually developing SLE. Immunosupression is the initial therapeutic option, but up to one fifth of patients do not respond and require splenectomy**.** ***(Sultan et al .,2003)***

G. Gastrointestinal:

The gastrointestinal (GI) and hepatobiliary systems are susceptible in their entirety to SLE-related complications. GI symptoms are very common and may result from SLE, treatment, or non-SLE etiologies, and differentiating the true cause of symptoms may herald a diagnostic nightmare for clinicians and delay institution of the appropriate intervention. Oral ulcers are the only GI manifestation to be included in the ACR diagnostic guidelines for SLE, and occur in 7%–52% of patients. They are mostly painless and appear unrelated to systemic disease activity. Sjorgen's syndrome has a consistently reported prevalence of approximately 10%. Esophageal symptoms are commonly reported, with 1%–13% and 11%–50% of SLE patients experiencing dysphagia and heartburn, respectively. Manometry studies have revealed a frequent prevalence of peristaltic dysfunction, particularly within the upper third of the esophagus, which may explain some symptoms. However, no

studies have shown lower esophageal sphincter abnormalities, and it appears SLE patients are not at an increased risk of gastroesophageal reflux. Gastric disease resulting from SLE is controversial. Peptic ulcer disease or gastric perforation may occur as a consequence of NSAID and corticosteroid usage, rather than directly from SLE itself**..*(Sultan et al ., 1999 ;Manoussakis et al ., 2004)***

Acute abdominal pain (AAP) is reported by up to 40% of SLE patients, some of whom go on to present to hospital. Immunosuppressive drugs mask symptoms and signs, making accurate diagnosis difficult with resultant treatment delays. The treatment of most SLE-related causes of AAP is with high-dose corticosteroids or other immunosuppressive drugs,while non-SLE causes may require surgery. SLE causes of AAP include serositis, vasculitis, ischemic gut, pseudo-obstruction, pancreatitis, acalculous cholecytitis, and protein losing enteropathy. Treatment related causes include peptic ulcer disease ,intra-abdominal sepsis, infective enteritis or colitis, and pancreatitis. Most recent studies attribute the majority of AAP to non-SLE related causes,

and of SLE causes, intestinal vasculitis is the main culprit. ***(Vergara-Fernandez et al ., 2009)***

Hepatobiliary involvement in SLE is predominantly manifested as subclinical increases of liver function tests (LFTs) and may be attributable to drug treatment, including herbal medicines***.(Her et al ., 2009)***

Up to 60% of SLE patients have abnormal LFTs at some point in their illness, and of these approximately one fifth have no cause found except for the concomitant presence of SLE. Autoimmune hepatitis is rarely associated with SLE, with a lifetime prevalence of 2%–5% among SLE patients and is treated with high-dose corticosteroids. Hepatic thromboembolic complications have also been reported. Pancreatitis has an unclear association with SLE, and when it does occur, it appears to be more commonly of the idiopathic type and associated with disease activity. In patients with SLE and pancreatitis, active lupus has been associated with increased mortality**. *(Nesher et al ., 2006)***

H. Musculoskeletal:

Nonerosive arthritis is a hallmark of SLE, but other significant musculoskeletal complications are noteworthy. Osteoporosis is a major cause

of morbidity and is probably related to a combination of treatment complications and disease mechanisms, and secondary behavior, such as reduced physical activity and sunlight avoidance, may also contribute. The prevalence of osteoporosis has been reported to be as high as 23%, and one study reported a prevalence of fracture risk of 12.5%.***(Lee et al ., 2007)***

Interestingly, the relationship between corticosteroid usage and bone loss is not straight forward. Multiple studies have failed to show a relationship between corticosteroid usage and bone mineral density, whereas a stronger correlation is found with damage accrual scores, regardless of corticosteroid use. This supports the theory of disease-dependent loss of bone marrow density and that corticosteroid usage that suppresses SLE activity may be beneficial***.(Sinigaglia et al ., 2006)***

Almehed et al.(2007) prospectively assessed 59 patients, and 5 (8.5%) were found to have anterior atlanto- axial subluxation in full flexion cervical radiographs. Four of the 5 patients had neck pain, which was severe in only 1 person with concomitant paresthesia and hypoesthesia of the fingers. The patients with cervical subluxation had longer disease duration, chronic renal

failure, and higher serum parathyroid levels. The issue of cervical spine instability has never been fully studied in any large studies and remains an area of concern for anesthesiologists.

I. Infection:

SLE patients suffer a higher rate of infections, which appears related to both an intrinsic susceptibility and treatment- related immunosuppression. Immunological dysfunction may be due to functional asplenia, impaired complement system, and mannose-binding lectin deficiency, a serum protein that binds mannose in the bacterial wall and activates the complement system, although data are conflicting**.** ***(Kang and Park , 2003)***

The majority of infections are bacterial and primarily affect the skin, respiratory system, and urinary tract. SLE patients who develop infections require significantly longer hospitalization, and long-term survival is dramatically impacted by a single episode of bacteremia***.(Chen et al ., 2008)***

Factors predictive of infection in SLE patients include active disease, duration of disease, cytopenia, hypocomplementemia, renal involvement, CNS involvement, and immunosuppressive therapy. Multiple factors may

contribute to the innate infection susceptibility among these patients, including depressed production of interleukin-12, reduced serum complement, and antigranulocyte antibodies**.** ***(Ramos-Casals et al ., 2008)***

Viral infections in SLE are more likely to mimic a lupus flare and are often diagnosed after failure to respond to SLE-targeted therapy. Typical viral features of arthralgia, rash, fever, malaise, lymphadenopathy, and cytopenia are easily confused with lupus flares. Parvovirus B19 and cytomegalovirus are the most common viral infections, although many other viruses also cause morbidity. In those with SLE, parvovirus preferentially affects immunocompetent patients, whereas cytomegalovirus affects the immunosuppressed ***. (Jeong et al ., 2009)***

J. Cutaneous

Skin lesions in patients with SLE are classified as those for lupus-specific disease e.g., malar rash, and those for lupus non-specific disease e.g., alopecia (Gilliam classification).

There is great variation in incidence, clinical heterogenecity, and severity of disease between different ethnic and racial groups due to environmental,

cultural, and genetic variability. Diversity was also noted in the type of skin involvement ranging from classical butterfly rash, discoid lupus to bullae, alopecia, vasculitic rashes, etc **.**

Cutaneous lesions are important as a diagnostic aid as these account for 4 out of 11 revised ACR criteria for disease classification. Moreover, lupus-specific skin lesions serve primarily as an important diagnostic clue whereas lupus non-specific skin lesions are associated with more active disease and thus require more aggressive therapy and disease monitoring**.** ***(Zeevi et al ., 2001)***

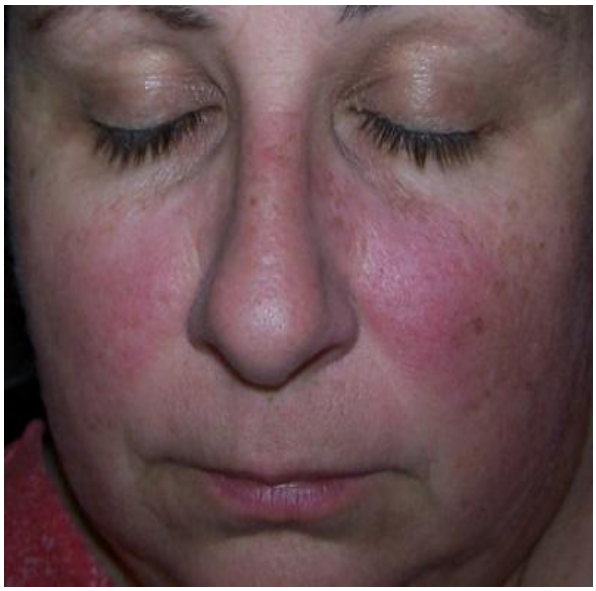

Fig.2 : Butterfly sign

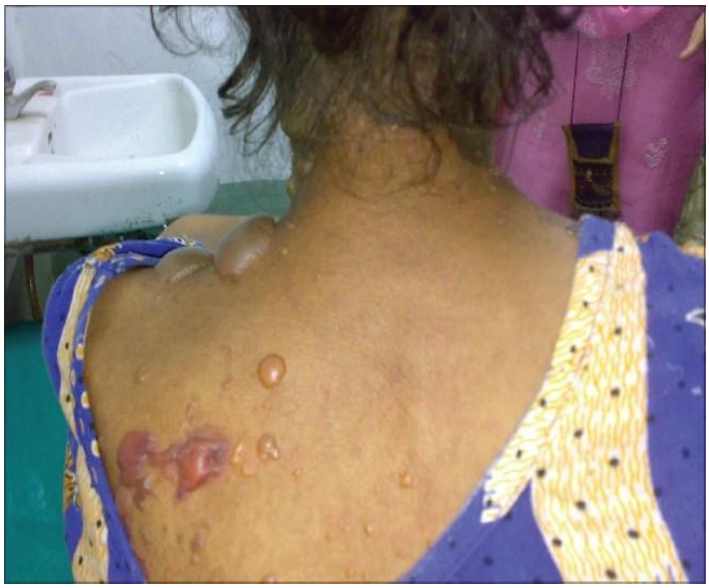

Fig.3: SLE with bullous lesions

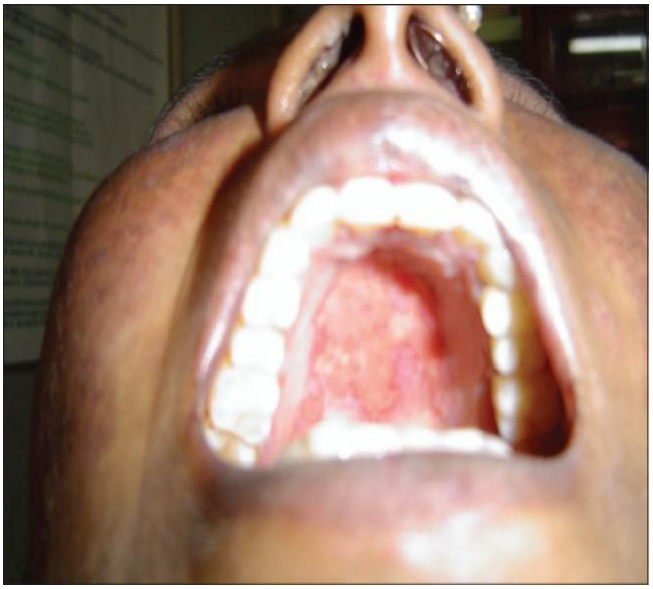

Fig.4: Oral Ulcers

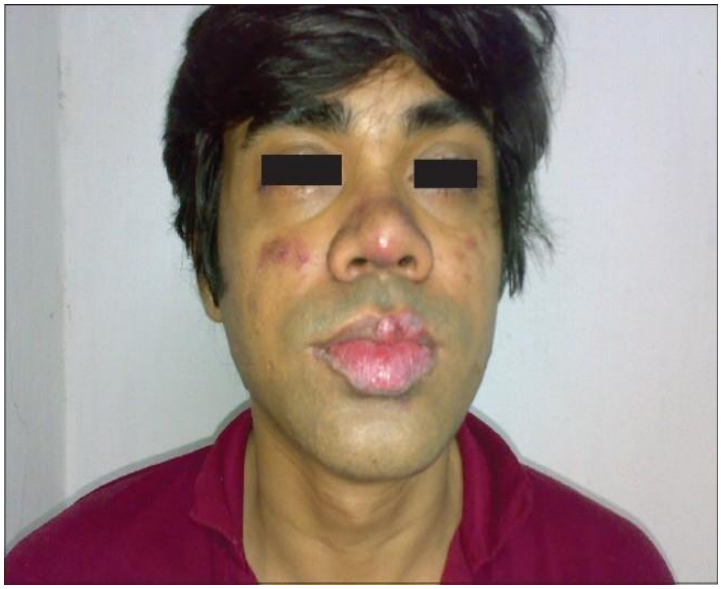

Fig.5: Malar rash and lip DLE

Figures (2-5): Cutaneous Manifestations of SLE (***Kole and Ghosh, 2009)***

Serological Diagnosis:

While the hallmark of SLE is the presence of antinuclear antibodies, a number of laboratory abnormalities characterize lupus. Serologically, the production of various autoantibodies is the immunopathologic basis of disease. A positive ANA perhaps the most important finding to establish initially, as this implicates auto immunity. However, a positive ANA is nonspecific and can be found in 5-20% of the normal population.

Anti-Sm antibodies are also diagnostic of SLE, seen with a frequency of 30-40%. Conversely, ANA-negative lupus, while extremely rare, may exist. Antibodies to double- stranded DNA(dsDNA) are found in 40-60% of SLE patients. They are associated with renal involvement but do not correlate well with disease activity. In fact, in a prospective study, anti-dsDNA levels fell on the day of a flare, possibly owing to deposition of antibodies in the tissues at the peak of clinical disease ***(HO et al., 2001).***

Therefore, while patients with elevated levels of anti-dsDNA over many years of disease have a poorer prognosis compared to those who do not, acute changes in the titers of anti-dsDNA do not predict disease flare at the next

clinic visit. Antiphospholipid antibodies may also be found in lupus (50%) and can cause venous and arterial thrombosis, as well as recurrent fetal loss. Assessment is by the detection of antibodies to cardiolipin or to beta-2 glycoprotein 1, or by the presence of a lupus anticoagulant, which is marked by prolonged clotting times that are not corrected by mixing studies *in vitro*. Autoantibodies lead to the formation of immune complexes, which activate and consume complement. Hence, measuring levels of C3, C4, or total hemolytic complement CH50 may be helpful in the diagnosis of lupus, as well as in the routine monitoring of SLE patients. However, hypocomplementemia is not specific to SLE and can be found in any disease in which there is a large antigen-antibody load. ***(Esdaile et al., 2001)***

Prospective studies have not found changes in C3 or C4 to predict overall disease activity, but they were reduced with hematologic and renal flares on the same day the flare occurred .Hematologic abnormalities are common findings in SLE. Anemia may reflect chronic inflammation, renal disease, iron deficiency or gastrointestinal loss. In addition, an autoimmune, hemolytic anemia caused by autoantibodies against red blood cell antigens (Coombs positivity) can occur .An appropriate reticulocytosis excludes marrow

suppression as the underlying etiology of the anemia. Leukopenias and thrombocytopenias are common in SLE patients. They are thought to be secondary to antibodies directed against cell surface antigens. As with the other cytopenias, infection,malignancy, and adverse drug effects need to be ruled out.***(Voulgarelis et al .,2000)***

The ACR Classification of SLE:

Eleven classification criteria are identified that reflect the major clinical manifestations of the disease, including mucocutaneous , articular, serosal, renal, neurologic, hematologic, and immunologic features. The presence of 4 or more of these criteria, either serially or simultaneously and during any interval of observation, identifies a patient as having SLE for research purposes***. (Hochberg ,1997)***

The Systemic Lupus International Collaborating Clinics (SLICC) is an international group dedicated to SLE clinical research. This group produced tools that form the basis of outcome studies in SLE today, such as the SLICC-ACR Damage Index .***(Gladman et al .,1996)***

Updated Classification:

Concerns about the clinical criteria in the ACR classification including : possible duplication of highly correlated cutaneous lupus terms (such as malar rash and photosensitivity) and the absence of inclusion of many other lupus cutaneous manifestations; omission of many SLE neurologic manifestations; and the need to utilize new standards in the quantification of urine protein.

Concerns about the immunologic criterion included the omission of low complement, and the need to include new knowledge on antiphospholipid antibodies. Most of all, there were concerns about patients without any immunologic criteria being classified as SLE (an autoantibody-mediated disease). Indeed clinical trials have had to add the requirement for the presence of a SLE autoantibody when recruiting patients to optimize the likelihood of response to immunosuppressive therapy .***(Navarra et al .,2011)***

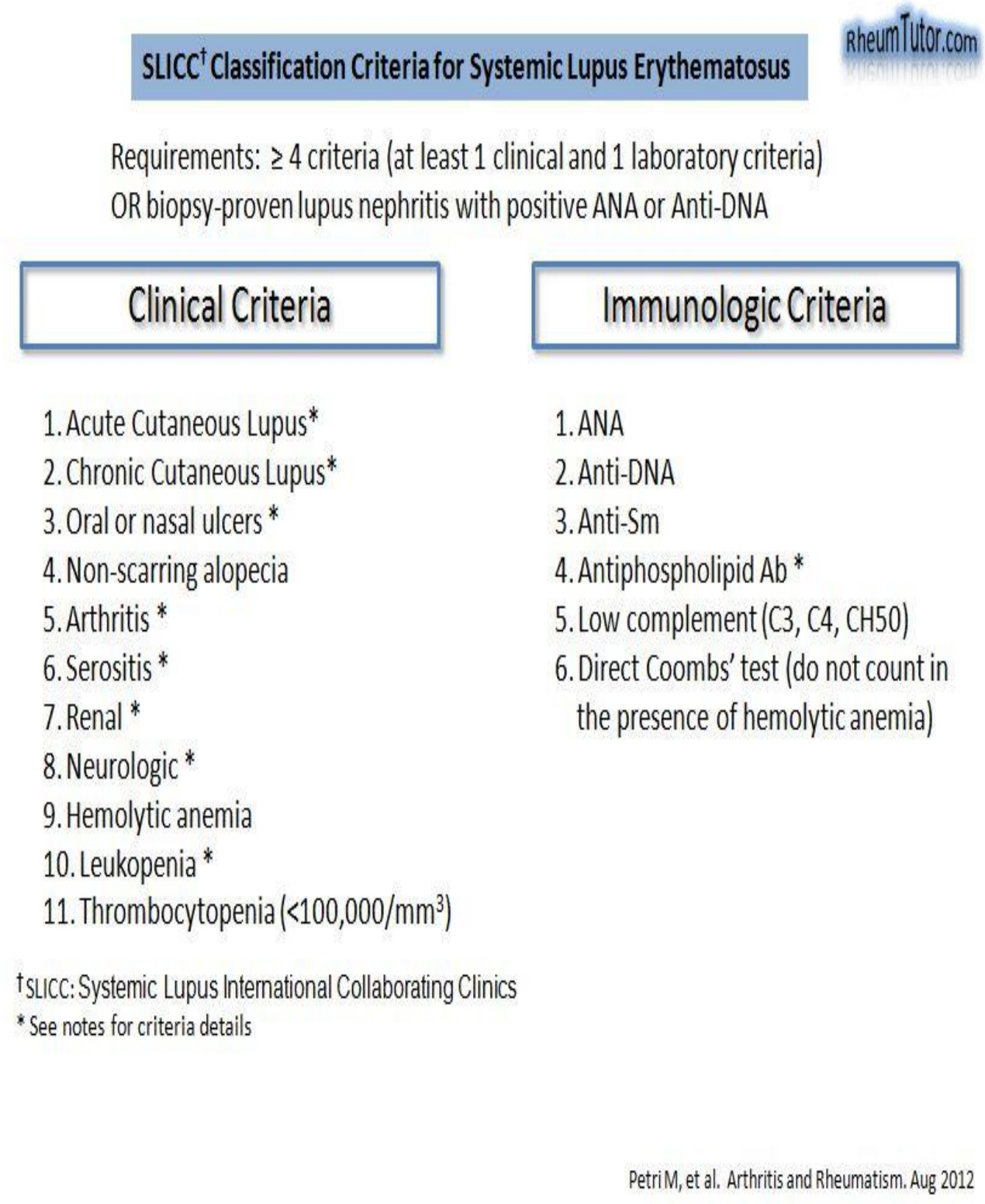

Fig 6: SLICC ***(Petri et al .,2012)***

Management of SLE:

Management of systemic lupus erythematosus (SLE) often depends on disease severity and disease manifestations, although hydroxychloroquine has a central role for long-term treatment in all SLE patients. The LUMINA (Lupus in Minorities: Nature versus Nurture) study and other trials have offered evidence of a decrease in flares and prolonged life in patients given hydroxychloroquine, making it the cornerstone of SLE management ***(Alarcón et al., 2007)***

In general, cutaneous manifestations, musculoskeletal manifestations, and serositis represent milder disease, which may wax and wane with disease activity. These are often controlled with nonsteroidal anti-inflammatory drugs (NSAIDS) or low-potency immunosuppression medications beyond hydroxychloroquine and/or short courses of corticosteroids. More prolonged steroid use is generally reserved for patients with involvement of vital organs. For example, central nervous system involvement and diffuse proliferative renal disease must be recognized as more severe disease manifestations, and these are often treated with more aggressive immunosuppression. Evidence suggests a relative undertreatment of SLE patients with end-stage renal

disease (ESRD), because the extent of lupus activity may be underestimated.***(Broder et al., 2011)***

EULAR Recommendations:

In 2007, the European League Against Rheumatism (EULAR) released recommendations for the treatment of SLE. In patients with SLE without major organ manifestations, glucocorticoids and antimalarial agents may be beneficial ***(Bertsias et al., 2008)***.

NSAIDs may be used for short periods in patients at low risk for complications from these drugs. Consider immunosuppressive agents (azathioprine, mycophenolatemofetil , methotrexate) in refractory cases or when steroid doses cannot be reduced to levels for long-term use***.(Mosca et al., 2010)***

EULAR recommendations for the management of SLE with neuropsychiatric manifestations support the evaluation and treatment of these symptoms in the same way as they are evaluated and treated in patients without SLE; if

symptoms persist, management of these symptoms as an extension of SLE should be considered. For example, in patients with neuropsychiatric manifestations that may have an inflammatory etiology, immunosuppressive agents may be considered ***(Bertsias et al., 2008)***

Adjunctive therapies:

Vitamin D insufficiency and deficiency are more common in patients with SLE than in the general population. Vitamin D supplementation may decrease disease activity and improve fatigue. In addition, supplementation may improve endothelial function, which may reduce cardiovascular disease ***(Zheng et al., 2016)***

No diet-based treatment of SLE has been proven effective. Patients with SLE should be reminded that activity may need to be modified as tolerated. Specifically, stress and physical illness may precipitate SLE flares. Additionally, persons with SLE should wear sunscreen and protective clothing or avoid sun exposure to limit photosensitive rash or disease flares ***(Reynolds et al., 2016)***

Assessment of SLE Activity

Assessing disease activity in SLE is crucial to the physician as it forms the basis for treatment decisions. Disease activity needs to be distinguished from damage as this has important implications for the long term prognosis and the appropriate treatment. Several validated global and organ-specific activity indices are widely used in the evaluation of SLE patients ***(Urowitz and Gladman,1998).***

The accepted measures of disease activity in SLE include erythrocyte sedimentation rate (ESR), plasma/serum complement component 3 (C3) and component 4 (C4) and presence of antibodies to double-stranded DNA (anti-dsDNA). Some patients, however, have abnormalities in these tests for considerable periods yet show few clinical symptoms or functional deterioration of a major organ; others are markedly symptomatic with only minor aberrations in these test results ***(Rahman and Hiepe , 2002)***

When evaluating the patient and assessing disease activity, there are generally three

patterns of disease to consider:

- Intermittent disease flares (or relapsing and remitting disease)

- Chronically active disease
- Quiescent disease

Disease activity refers to the reversible manifestations of the underlying inflammatory process at a point in time in terms of magnitude and intensity. The disease severity refers to the type and level of organ dysfunction and its consequences. The degree of irreversible organ dysfunction has been referred to as damage. In clinical practice, disease activity and severity are assessed using a combination of clinical history, physical examination, organ- specific tests, and serologic studies**.** ***(Illei et al., 2010)***

Clinical Evaluation

Given the heterogeneity of disease presentation and clinical course among patients with SLE, an assessment of disease activity should be performed at each clinic visit. Furthermore, features attributable to active SLE must be distinguished from chronic damage, drug toxicities, and other comorbidities such as infection. As an example, marked proteinuria and a reduced glomerular filtration rate may result from either active inflammation or scarred glomeruli. Differentiating between these two possibilities has significant therapeutic implications, since immunosuppressive therapy should

not be escalated in the latter setting. Similarly, joint pain may be related to active synovitis for which glucocorticoids may be indicated, or it may be due to avascular necrosis which is a side effect of treatment with glucocorticoids.

As part of the clinical and laboratory evaluation, all organ systems must be reviewed since almost any organ can be involved in SLE. If specific symptoms are present, patients should also be asked about any potential triggers such as sun exposure, infection, or discontinuation of therapy***.(Jolly ,2010)***

The physical examination should be extensive (complete) and include examination of the skin (including scalp and mucous membranes) and lymph nodes, as well as respiratory, cardiovascular, abdominal, musculoskeletal, and neurologic systems. A variety of validated indices have been developed primarily for research purposes to measure disease activity or damage; however, their incorporation into clinical practice is often limited by the time needed to complete them***. (Liu et al., 2013)***

Laboratory Evaluation

In addition to obtaining a detailed clinical history and performing a thorough physical exam, laboratory tests may be used to help assess disease activity and monitor organ-specific complications (such as renal or hematological). Since there is no single marker of disease activity, clinicians must interpret the laboratory results in the appropriate clinical context. The following laboratory tests are often used when monitoring disease activity in all patients with SLE:

● Complete blood count (CBC) : Leukopenia is common and may reflect active disease.

Anemia and thrombocytopenia may also be observed with active disease.

Cytopenias may also result from drug toxicities.

● Acute phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) : Increases in acute phase reactants are commonly observed in patients with SLE, and therefore may not be as reliable for detecting disease activity as is the case with other inflammatory diseases. Nonetheless, an elevated ESR can be associated with increased disease activity and accrued damage. Similarly, elevations in CRP can also be associated with disease activity. There are conflicting data on the diagnostic value of a markedly

elevated CRP in distinguishing active lupus from infection; however, an elevated CRP should raise the suspicion for infection in a patient with SLE.

● Urine analysis with examination of urinary sediment : Proteinuria or cellular casts and hematuria may be due to lupus involving the kidney.

● Spot (untimed) urine protein and creatinine: Quantification of proteinuria helps assess the severity of glomerular disease.

● Serum creatinine and estimated glomerular filtration rate (eGFR) : Elevations in serum creatinine may reflect lupus nephritis.

● Anti-double-stranded deoxyribonucleic acid (dsDNA) : Titers of anti-sDNAantibodies often fluctuate with disease activity, particularly in patients with active glomerulonephritis.

●Complement levels (C3 and C4) : Low complement levels often indicate active lupus, particularly lupus nephritis ***..(Stojan et al., 2013)***

Measurement of disease activity in systemic lupus erythematosus is central to clinical research when evaluating clinical outcome comparing meaningful differences among SLE patient groups, and assessing disease activity

longitudinally for observational and clinical trials. Several reliable and validated instruments have been available since the early 1980s, and some updated measures are now being used in clinical trials for classifying and monitoring groups of patients and gauging responses to a new drug ***(Petri et al., 2012)***

The administrative burden of the disease activity measure with its intricate psychometric properties needs to be taken into consideration when choosing an instrument applicable in a particular research or clinical setting. The administrative burden expands beyond the knowledge about the instrument itself to include the preparedness and skillfulness of the assessor, the mode of administration, the time required to complete the instrument, and the complexity of scoring. Furthermore, the varied length of the scales (number of items and scoring scale), number of patients included, or disease severity of patients under study influence the performance across proposed instruments and weigh into the administrative burden through required advanced training and familiarity of the instrument.(***Rahman and Isenberg , 2008***)

The Outcome Measures Rheumatology group and the US Food and Drug Administration (FDA) had recommended using measures of disease activity, cumulative organ damage, health-related quality of life (HRQOL), and adverse events as outcomes of interest**.** ***(D'Cruz et al., 2007)***

Patient-reported outcome measures broadly classified as descriptive, discriminative, evaluative, or predictive or a combination of these are being incorporated in clinical trials yet still await further adaptation and validation to reflect an accurate measure of any intervention. Responsiveness remains a key element of the psychometric properties of any instrument. It is pivotal to identify and validate appropriate global, disease-specific, and perhaps organ-specific health-related outcomes for clinical research***.(Arbuckle et al., 2003)***

Major Disease Activity Measures

British Isles Lupus Assessment Group (BILAG) and BILAG 2004.

The BILAG index, an organ-based transitional activity instrument, provides disease activity scorings across eight organ systems on an ordinal scale (A to E) based on the physician's intention to treat premise***.(Edworthy , 2005)***

The original version was published in 1988, and the updated version (BILAG-2004) was published in 2005. In the revised index, the original section of vasculitis was removed and two systems were added: ophthalmic and abdominal.

The BILAG-2004 index categorizes disease activity into five different levels from A to E:

(Grade A) represents very active disease likely necessitating immune - suppressive drugs and/or a prednisolone (or equivalent) dose of more than 20 mg daily or high-dose anticoagulation. (Grade B) represents moderate disease activity requiring a lower dose of corticosteroids, topical steroids, topical immunosuppressive drugs, anti-malarials, or non-steroidal anti-inflammatory drugs. (Grade C) indicates mild stable disease, and (grade D) implies no

disease activity but suggests the system had previously been affected. (Grade E) indicates no current or previous disease activity.***(Griffiths et al., 2010)***

SLE Disease Activity Index and Its Versions

The SLEDAI is a global index that was developed and introduced in 1985 as a clinical index for the assessment of lupus disease activity in the preceding 10 days. It consists of 24 weighted clinical and laboratory variables of nine organ systems. This instrument was derived by consensus among experts in rheumatology followed by application of regression models to assign relative weights to each parameter.(***Bombardier et al.,1992)***

SLEDAI was modeled on the basis of clinician global judgment. The scores of the descriptors range from 1 to 8, and the total possible score for all 24 descriptors is 105***(Lo and Tsokos , 2011)***

Measuring SLE Flares

Several studies have attempted to define flare, including time to flare, numbers of flares, and severity of flares. Optimal SLEDAI cutoffs for active disease and flare, based on a physician's expert opinion, have been examined. Flare was defined as a 4-point increase in SLEDAI-2 K.The SELENA-SLEDAI Flare Index (SFI), developed by the SELENA trials, is a composite outcome of SELENA-SLEDAI; mild, moderate, and severe flares; and the physician global assessment (PGA) of disease activity. The revised SFI suggests specific clinical manifestations for each organ system and categorizes flares into mild, moderate, and severe on the basis of the treatment decision. ***(Petri et al., 2012)***

The SLEDAI Variables are shown in Figure 7

Wtd score	Descriptor	Definition.
8	Seizure	Recent onset. Exclude metabolic, infectious, or drug-related causes.
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Includes hallucinations; incoherence; marked loose associations; impoverished thought content; marked illogical thinking; bizarre, disorganized or catatonic behavior. Exclude the presence of uremia and offending drugs.
8	Organic brain syndrome	Altered mental function with impaired orientation or impaired memory or syndrome other intellectual function, with rapid onset and fluctuating clinical features. Includes a clouding of consciousness with a reduced capacity to focus and an inability to sustain attention on environment, and at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, increased or decreased psychomotor activity. Exclude metabolic, infectious, and drug-related causes.
8	Visual	Retinal changes from systemic lupus erythematosus: cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, optic neuritis (not due to hypertension, drugs, or infection).
8	Cranial nerve	New onset of a sensory or motor neuropathy involving a cranial nerve.
8	Lupus headache	Severe, persistent headache; may be migranous; unresponsive to narcotics.
8	Cerebrovascular accident	New syndrome. Exclude arteriosclerosis.
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages. Vasculitis confirmed by biopsy or angiogram.
4	Arthritis	More than 2 joints with pain and signs of inflammation .
4	Myositis	Proximal muscle aching or weakness associated with elevated creatine phosphokinase/aldolase levels, electromyographic changes, or a biopsy showing myositis.
4	Casts	Heme, granular, or erythrocyte.
4	Hematuria	More than 5 erythrocytes per high power field. Exclude other causes (stone, infection).
4	Proteinuria	More than 0.5 grams of urinary protein excreted per 24h. New onset or recent increase of > 0.5 g/24h.
4	Pyuria	More than 5 leukocytes per high-power field. Exclude infection.
2	New malar rash	New onset or recurrence of an inflammatory type of rash.
2	Alopecia	New or recurrent. Apatch of abnormal, diffuse hair loss.
2	Mucous membranes	New onset or recurrence of oral or nasal ulcerations.
2	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	Pericarditis	Pericardial pain with at least one of rub or effusion. Confirmation by electro- or echocardiography.
2	Low complement	Adecrease in CH50, C3, or C4 level (to less than the lower limit of the laboratory-determined normal range).
2	Increased DNAbinding	More than 25% binding by Farr assay (to >the upper limit of the laboratory-determined normal range, e.g. 25%).
2	Fever	More than 38 ºC after the exclusion of infection.
2	Thrombocytopenia	Fewer than 100,000 platelets
2	Leukopenia	Leukocyte count of < 3000/mm^3 (not due to drugs)

Adapted from Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 1992; 35: 630-40.

Fig.7 SLEDAI Index ***(Bombardier ., et al 1992)***

SLEDAI-2000

SLEDAI-2000 (SLEDAI-2 K) was introduced in 2002 as a measure of global disease activity. SLEDAI-2 K is a modification of the original SLEDAI to allow the documentation of persistent disease activity in the descriptors: rash, alopecia, mucosal ulcers, and proteinuria. SLEDAI-2 K has been validated against the classic SLEDAI, and proven to be sensitive to change over time. SLEDAI is a strong predictor of mortality in SLE ***(Hanly et al., 2011)***

NLR and PLR , definition , overview and recent studies

White blood cell count and its classification have been reported as inflammatory markers in chronic inflammatory diseases ***(Ahsen et al ., 2013)***

Neutrophilia and lymphocytopenia are typical phenomena of the innate immune response to various stressful insults. Relation of neutrophils and lymphocytes during the development of systemic inflammatory response expressed as NLR (ratio of neutrophils to lymphocyte counts in absolute or relative values) is a simple, rapid and reliable method of how to evaluate the extent of stress or systemic inflammation. NLR can be used routinely indaily clinical practice of intensive medicine ***(Zahorec , 2001)***

Platelets mediate tumor cell growth, dissemination and angiogenesis. In turn, tumor cells induce platelet aggregation, which is known to be the trigger for the development of cancer-associated thrombosis ***(Goubran et al ., 2014)***

Tumors are known to produce myeloid growth factors, including granulocyte colony-stimulating factor, tumor necrosis factor-α, interleukin (IL)-1and IL-6, which may increase the number of neutrophilic granulocytes at the site of the tumor ***(Kwon et al ., 2012)***

Neutrophilia promotes tumor growth and metastasis by remodeling the extracellular matrix and releasing reactive oxygen species, nitric oxide and arginase, which suppress the T cell response and increases the rate of mutagenesis ***(Azab et al ., 2013)***

Platelets also regulate angiogenesis by releasing numerous proangiogenic proteins, including vascular endothelial growth factor, and aid the maintenance of vascular integrity, therefore facilitating tumor cell survival and growth ***(Liu et al ., 2013)***

Platelets shield tumor cells from host immune surveillance and direct cellular contact with natural killer cells by inducing platelet mimicry and constructing a mesh with fibrin that surrounds tumor cells within the vasculature during hematogenous dissemination ***(Asher et al., 2011)***

Platelets recruited to the tumor micro-environment consequently release platelet-derived growth factor and transforming growth factor to promote tumor growth ***(Sharma et al., 2014)***

Tumor cells possess the ability to manipulate platelet activity to optimize tumor growth, proliferation, survival and metastasis. Several studies have identified the association between a poor survival rate and elevated PLR in solid tumors ***(Templeton et al ., 2014)***

Absolute lymphocytopenia can be used in the prediction of infectious emergency admissions. Moreover, the ratio of neutrophil and lymphocyte counts referred to as the NLR has even higher value in predicting bacteremia This marker is simple, easily obtained and calculated،easy to integrate in daily practice and without extra costs ***(De Jager et al ., 2010)***

The neutrophil-to-lymphocyte ratio (NLR) is a simple ratio of the absolute neutrophil and lymphocyte counts obtained on the differential section of the total white blood cell count (WBC) of a complete blood cell (CBC) count. NLR is a marker of inflammatory response and has been shown to be associated with poor outcomes in patients with several types of disease. A high NLR was associated with an adverse overall survival in many solid tumors in a systematic review and the NLR had independent prognostic value in various clinical utilities for pa-tients with cancer ***(Grivennikov et al ., 2010)***

NLR should be taken into account as quick, cheap, easily measurable, new inflammatory marker, instead of other acute-phase proteins, such as CRP in Familial Mediterranean Fever ***(Ahsen et al ., 2013)***

In the cardiovascular system, the NLR has correlated with worse results in patients with acute coronary syndrome and coronary heart disease and can independently predict coronary heart disease in an asymptomatic general population cohort ***(DeNardo and Coussens , 2007)***

Krenn-Pilko et al.,(2014), proved that the NLR has shown to be a useful marker in kidney transplantation .Instead NLR and PLR, calculated from leukocyte differential counts and platelet counts, respectively, are more readily available and inexpensive compared to CRP .

Kulaksizoglu et al proved that NLR may be involved in inflammatory pathophysiology of schizophrenia. Further studies are needed to investigate the effect of antipsychotic treatment on NLR in drug-naive schizophrenic patients. It will also be of interest in future studies to determine whether NLR is different among schizophrenia subgroups . ***(Kulaksizoglu et al ., 2016)***

There are some meaningful correlations of NLR and PLR with inflammatory markers and severity in Atopic Dermatitis patients. ***Jiang and Ma,(2017)*** reached 3 conclusions :First, NLR and PLR were increased in patients with atopic dermatitis compared with the control group. Second, elevated NLR and PLR levels were linked to increasing SCORAD, which proves they can reflect inflammatory response and disease severity in AD patients. Third , NLR, which is easily calculated using the differential WBC count ،can be used as an indicator of the clinical severity of AD as recorded by the SCORAD index**.**

An elevated NLR or PLR is always accompanied by lymphopenia, which is caused by systemic inflammation and leads to the release of a number of inhibitory immunological mediators, particularly IL-10 and transforming growth factor-β. These inhibitory immunological mediators may exert an immunosuppressive effect with an impaired lymphocyte function ***(Salazar-Onfray et al ., 2007)***

NLR and PLR could be two new inflammatory markers indicating disease activity in patients with Reumatoid Arthritis (RA). If these results are supported by various prospective studies assessing NLR and PLR in patients

with RA، they can be classified among the other inflammatory markers used in the assessment of disease activity ***(Uslu et al., 2015)***

The NLR and the PLR of Heart Failure (HF) patients were higher than those of the age-sex matched controls. However, the NLR and the PLR were not sufficient to establish a diagnosis of HF. The NLR may be used in the HF patient follow-up to predict mortality ***(Durmus et al ., 2015)***

PLR is expressed as a marker for the diagnosis of acute appendicitis ***(Yazar et al ., 2015)***

Mean Platelet Volume (MPV) and PLR are useful in the clinical setting to assess the severity of hip Osteo-Arthritis ***(Taşoğlu et al ., 2017)***

The PLR in children with gastrointestinal bleeding is significantly higher than in those without gastrointestinal bleeding ***(Gayret et al., 2016)***

Both neutrophil counts and neutrophil /lymphocyte ratio were significantly correlated with non-calcified plaque burden and non-calcified plaque/total plaque ratio. The results highlight the potential utility of these easily measured

cellular markers in the risk assessment and monitoring of Coronary Artery Disease patients ***(Nilsson et al ., 2014)***

The global picture of inflammatory cytokines in End Stage Renal Disease (ESRD) patients is extremely complex. However, simple calculation of NLR can predict inflammation in this population **.** ***(Turkmen et al ., 2014)***

Neutrophilia suppresses lymphocyte activity, therefore counteracting the antitumor immune response ***(Lee et al ., 2013)***

An elevated NLR has been associated with a poor survival rate in breast, esophageal and gastric cancers ***(Jiang et al., 2014)***

Chiang et al.,(2012), demonstrated that patients with an elevated NLR (>3) in Colo Rectal Cancer (CRC) appeared to possess larger tumors and a more advanced tumor stage, and possessed a poorer 5-year disease-free survival rate

Liu et al.,(2013) reported that patients with CRC and a higher PLR possessed a significantly lower 5-year Overall Survival rate compared with patients with a low PLR, and identified pre-operative PLR as a clinically significant factor for the assessment of the prognosis of resectable CRC **.**

Zou et al.,(2016), approved that neutrophils and platelets are important in promoting CRC progression, but neutrophils are more crucial. Furthermore, adjuvant chemotherapy appeared to be more effective in CRC patients with a high NLR or PLR .

NLR and PLR were correlated with prognosis in patients with gastric cancer. Although this study was a retrospective analysis and a single-center study, it indicates the potential usefulness of a new predictor of the pathologic response to chemotherapy. The low cost and easy accessibility and reproducibility of a full blood count are other features promoting its use in clinical practice. ***(Lee et al ., 2013)***

NLR was usefull in the prediction of Overall Survival in patients with advanced stage bladder cancer. The NLR was thus found to be an independent prognostic marker for predicting the prognosis. The preoperative NLR predicted prognosis in patients who underwent radical cystectomy and might therefore function as a reliable biomarker for invasive bladder cancer ***(Lino-Silva et al ., 2016)***

An elevated NLR can identify patients at high risk for recurrence and cancer-specific death. Dominant pro-tumor activities of neutrophils or reduced anti-tumor immune response by lymphocytes, as determined by elevated NLR, may have a impact on poor tumor response and unfavorable prognosis in terms of recurrence and survival ***(Kim et al., 2014)***

Preoperative NLR and PLR and their normalization might be good markers for better disease control in patients with synchronous colorectal liver metastasis. PLR was better than NLR for predicting Progression-free survival in colorectal liver metastasis ***(Wu et al., 2016)***

An increased preoperative PLR seems to significantly affect Overall Survival in non-metastatic breast cancer patients and may support oncological therapy decisions. Clarifying the optimal PLR cutoff level and independent validation of our findings is warranted ***(Krenn-Pilko et al ., 2014)***

NLR at the time of diagnosis is predictive of overall survival and recurrence-free survival in patients of Hepato Cellular Carcinoma (HCC). Subsequently, the NLR might become a simple and non-invasive addition to the current allocation system for liver transplantation ***(Limaye et al ., 2013)***

Szkandera et al., (2014) revealed that an elevated PLR was significantly associated with a decreased time to recurrence and demonstrated a trend towards a decreased Overall Survival (OS) time in patients with stage II and III colon cancer that underwent curative resection **.**

The Aim of the work:

The aim of this study is to evaluate the value of neutrophil lymphocyte ratio and platelet lymphocyte ratio as simple and cheap prognostic markers of the activity of systemic lupus disease.

Patient and Methods

This study is a prospective study that is conducted on 60 patients diagnosed with Systemic Lupus Erythematosus in internal medicine department , Ain Shams University Hospitals and 30 control persons.

All cases are 60 as 59 female (98.33) and only 1 male (1.67). Active SLE cases are all females 30(100.0) . Remission cases are 30 as 29 female (96.7) and 1 male (3.3).Controls are 30 persons as 28 female and 2 males .Mean age of active SLE group is 28.0±9.04 , mean age of remission group is 27.73±7.6 and mean age of control group is 28.0±7.2. All cases and control age ranges from (16-45) taken from October 2016 till April 2017.

Patients' selection:

The study includes 90 persons divided into 3 groups as follows:

Group (I):

Includes thirty active SLE patients (newly diagnosed and resistant cases).

Group (II):

Includes thirty patients of SLE in remission.

Group (III):

Includes thirty healthy control persons

Inclusion criteria:

1. Patients diagnosed with SLE.

2. Patients aged 16 years or more.

Exclusion Criteria:

1. Patients diagnosed with other autoimmune diseases.

2. Patients with other known blood diseases that may affect the results.

3. Patients with hepatic or renal disease as platelet count may be affected.

All patients were subjected to the following:

1- Full history taking and clinical examination.

2- Laboratory investigations including:

A-Complete blood picture with differential count

Including :

1- HB%

2- Platelets

3- WBCs

4- Neutrophil count

5- Lymphocytes

6- Calculation of NLR and PLR.

B- Liver function tests as follow:

1- SGOT

2- SGPT

3- S.Albumin, total protein.

4- S.Total Bilirubin, direct and indirect.

C- Kidney function tests as follow:

1- S.Creatinine

2- BUN

3- Uric acid

4- Protein creatinine ratio.

5- Urine analysis

6- Serum Electrolytes.

D- Immune Markers and markers of activity including:

1- Antinuclear Antibody (ANA). Titre and Pattern.

2- Ani DNA with titre.

3- C3 and C4.

4- ESR and CRP

.

E- Serological viral markers (HBsAg, HCV Ab, HIV Ab).

Informed written consent were taken from all subjects enrolled in the study.

All results were collected, tabulated and discussed.

Statistical Analysis of the Data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent ·Quantitative data were described using median (minimum and maximum) for non parametric data and mean, standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the 5% level.

The used tests were

1 - Chi-square test

For categorical variables, to compare between different groups.

2- Student t test

For parametric quantitative variables, to compare between two studied groups.

3 - F-test (ANOVA)

For parametric quantitative variables, to compare between more than two studied groups.

4 - Mann Whitney test

For non-parametric quantitative variables, to compare between two studied groups .

5 – Kruskal Wallis test

For non parametric quantitative variables, to compare between more than two studied groups

6-Spearman correlation

For non parametric correlation between quantitative and ordinal variables.

7-Binary logistic regression

For detection of predictors of diseases status with Odds ratio calaculation

Results

The study recruited 60 patients with SLE and 30 control persons. They were subjected to careful history taking, thorough clinical and laboratory investigations including CBC , Liver and Kidney functions and immunological parameters as ANA , Anti-Ds DNA , C3 and C4.

The study includes 90 persons divided into 3 groups as follows:

Group (I):

Includes thirty active SLE patients (newly diagnosed and resistant cases).

Group (II):

Includes thirty patients of SLE in remission.

Group (III):

Includes thirty healthy control persons

Informed written consent were taken from all subjects enrolled in the study.

All results were collected, tabulated and discussed as follows:

Table (2) : Comparison between active (group I) , remission (group II) and control (group III) regarding demographic characters

parameters	**Group I n=30**	**Group II n=30**	**Group III n=30**	**Test of significance**
Age (years) Mean ± SD	28.0±9.04	27.73±7.6	28.0±7.2	F=0.25 P=0.8 p1=0.8 p2=0.7 p3=0.9
Sex	N(%)	N(%)	N(%)	
• Female	30(100.0)	29(96.7)	28(93.3)	χ^2=2.07 P=0.35
• Male	0(0.0)	1(3.3)	2(6.7)	

F:One Way ANOVA test for parametric quantitative variables

χ^2= Chi-Square test for categorical variables, to compare between different groups.

P: Probability

Table (2) showed that:

All cases are 60 as 59 female (98.33) and only 1 male (1.67).

Active SLE cases are all females 30(100.0) . Remission cases are 30 as 29 female (96.7) and 1 male (3.3). Control persons are 28 female (93.3) and 2 males (6.7).Mean age of active SLE group (group I) is 28.0±9.04 , mean age of remission group (group II) is 27.73±7.6 and mean age of control group(group III) is 28.0±7.2.

Table (3) : Comparison between active (group I) , remission (group II) and control (group III) regarding CBC results

parameters	**Active n=30 (group I)**	**Remission n=30 (group II)**	**Control n=30 (group III)**	**Test of significance**
Hb (gm/dl)	10.05±1.9 (7.4-14.3)	10.9±1.9 (7.3-15.5)	13.57±1.33 (11.6-16.4)	p1=0.085 p2<0.001** p3<0.001**
Platelet	327.0 (178.0-600.0)	256.5 (131.0-470.0)	256.5 (164.0-472.0)	p1=0.057 p2=0.007** p3=0.65
WBCS	7.45 (3.5-16.2)	7.2 (1.7-14.6)	6.1 (4.0-10.2)	p1=0.469 p2=0.04* p3=0.09
Neutrophil	5.18 (2.27-14.97)	4.53 (1.2-11.3)	3.55 (2.0-7.01)	p1=0.19 p2=0.014* p3=0.08
Lymphocytes	0.95 (0.31-2.48)	1.73 (0.51-3.48)	1.9 (1.1-2.9)	p1<0.001** p2<0.001** p3=0.84

All parameters described as median (min –max) except Hb described as mean ± SD(min-max)

Used test One Way ANOVA test for parametric with Post Hoc LSD , KruskalWallis test and Mann Whitney U test for non parametric variables

P1: difference between active SLE and SLE in remission, P2: difference between active SLE and Control group , P3:

difference between SLE in remission and Control group

*P: probability * p value significant if <0.05 ** p value high statistically significant <0.01*

Table (3) showed that:

Mean hemoglobin level of active SLE group (group I) (10.05±1.9) was significantly decreased compared to control group (group III) (13.57±1.33) , ($p<0.001$) . Moreover, the hemoglobin level of remission group (group II) (10.9±1.9) was significantly decreased than that of control group (group III) (13.57±1.33) , ($p<0.001$).Meanwhile, there was no statistically significant difference between active SLE group (group I) and remission group (group II), ($p=0.085$)

Median platelet count of active SLE group (group I), 327.0 (178.0-600.0) was significantly increased compared to control group (group III), 256.5 (164.0-472.0) $p=0.007$. Active SLE group (group I) had higher platelet count compared to remission group (Group II) ,but yet, not statistically significant, ($p=0.057$). Moreover, there was no statistically significant difference between remission group (group II) and control group (group III) , ($p=0. 65$).

Median WBCs count of active SLE group (group I) , 7.45(3.5-16.2) was significantly increased compared to control group (group III), 6.1(4.0-10.2)

p=0.04. But there was no statistically significant difference between active SLE group (group I) and remission group (group II) , (p=0.469). Moreover, remission group (group II) had higher WBCs count compared to control group (group III),but yet, not statistically significant, (p=0.09).

Median Neutrophil count of active SLE group (group I) , 5.18(2.27-14.97) was significantly increased compared to control group (group III),3.55(2.0-7.01) p=0.014. Active SLE group (group I) had higher neutrophil count compared to remission group (Group II) ,but yet, not statistically significant, p=0.19. Moreover, there was no statistically significant difference between remission group (group II) and control group (group III) , (p=0. 08).

Median Lymphocytes count of active SLE group (group I), 0.95(0.31-2.48) was significantly decreased compared to both, remission group (group II), 1.73(0.51- 3.48) , p1<0.001 and to control group (group III),1.9 (1.1-2.9), p2<0.001. Meanwhile, there was no statistically significant difference between remission group (group II) and control group (group III) p3=0.84

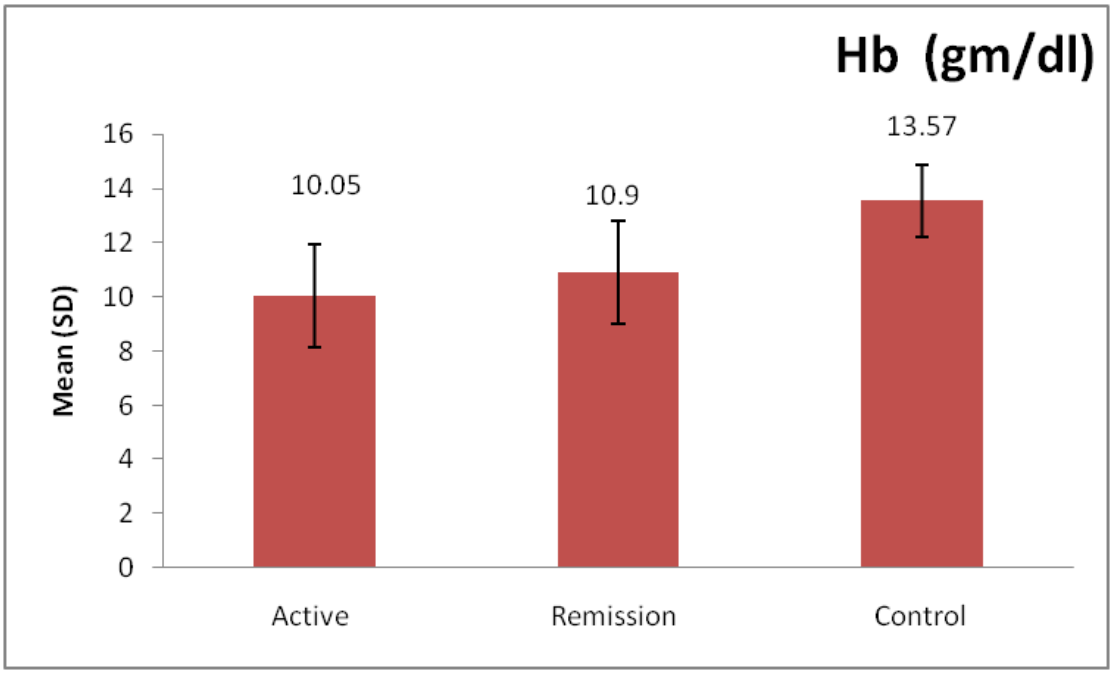

Figure 7 : comparison between groups as regard Hb%

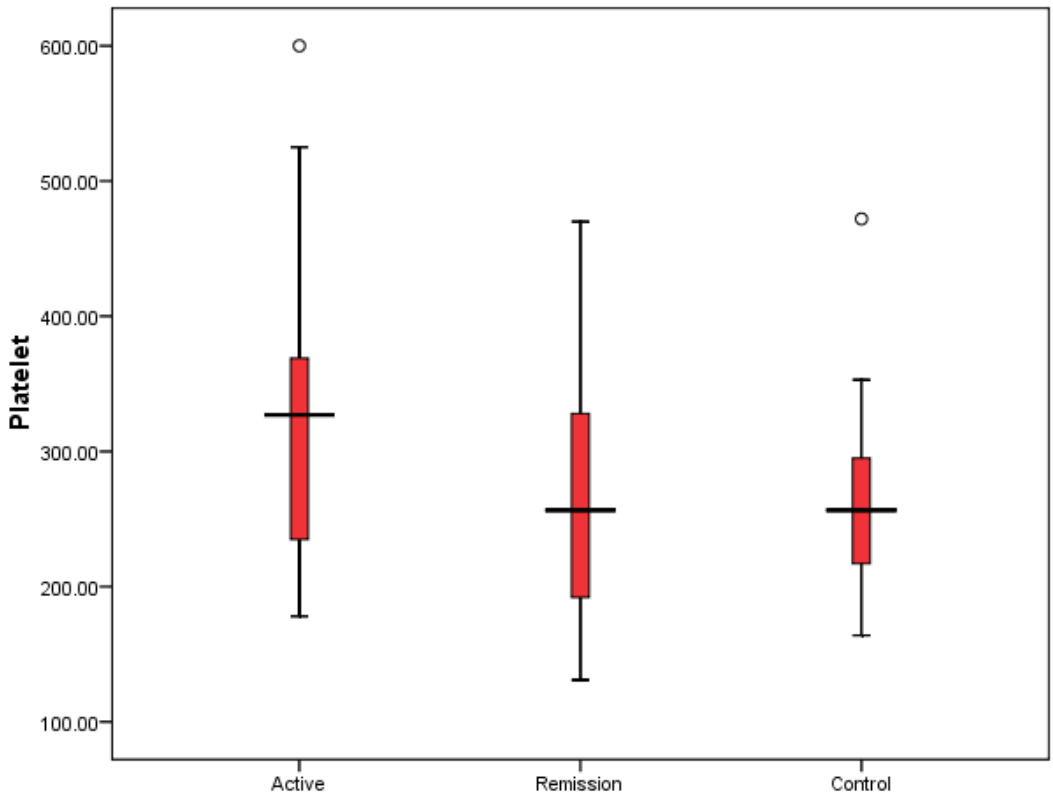

Figure 8: comparison between groups as regard Platelet count

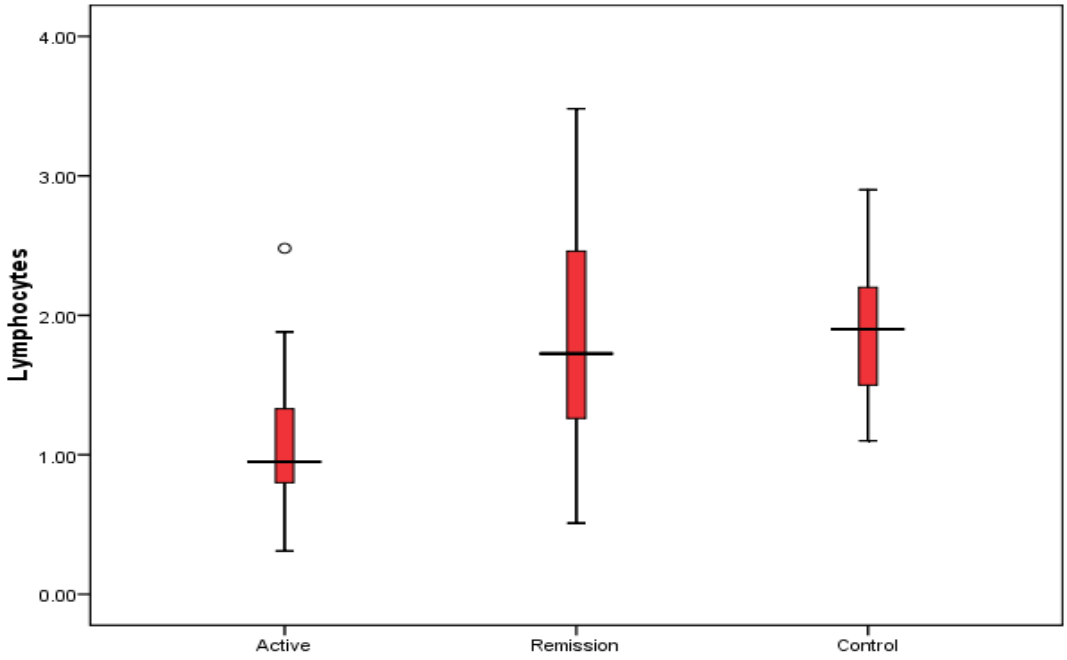

Figure 9: comparison between groups as regard Lymphocyte count

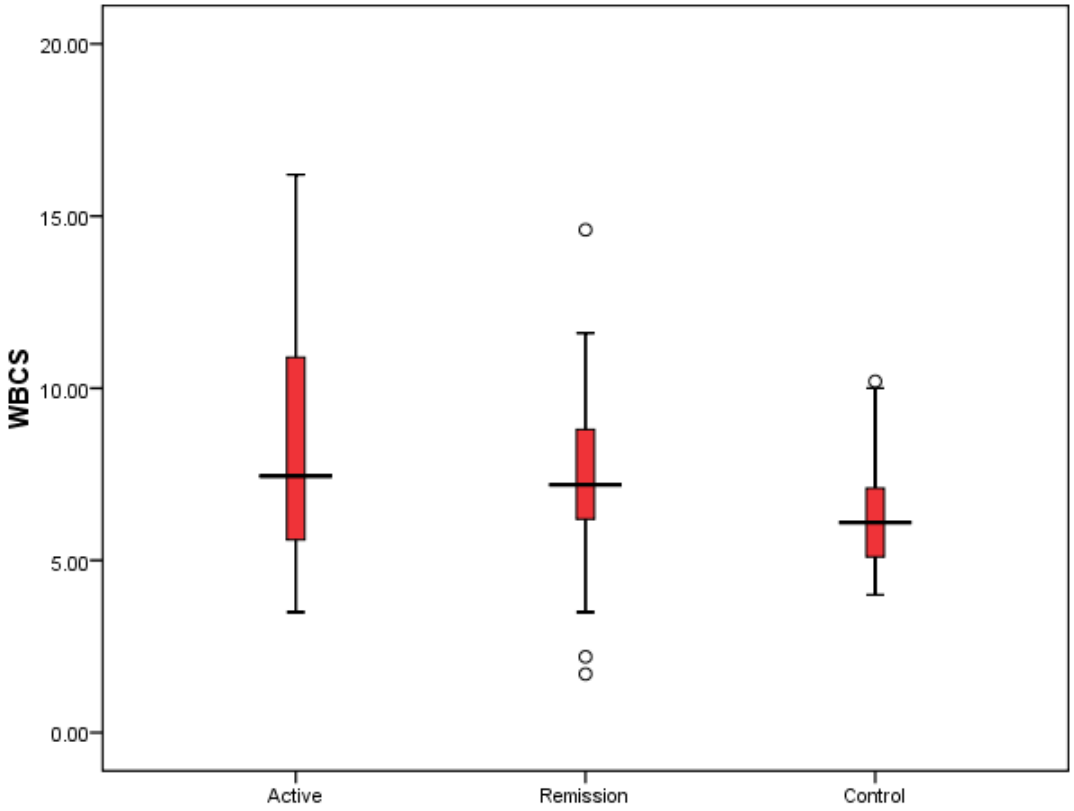

Figure 10: comparison between groups as regard White Blood Cell count

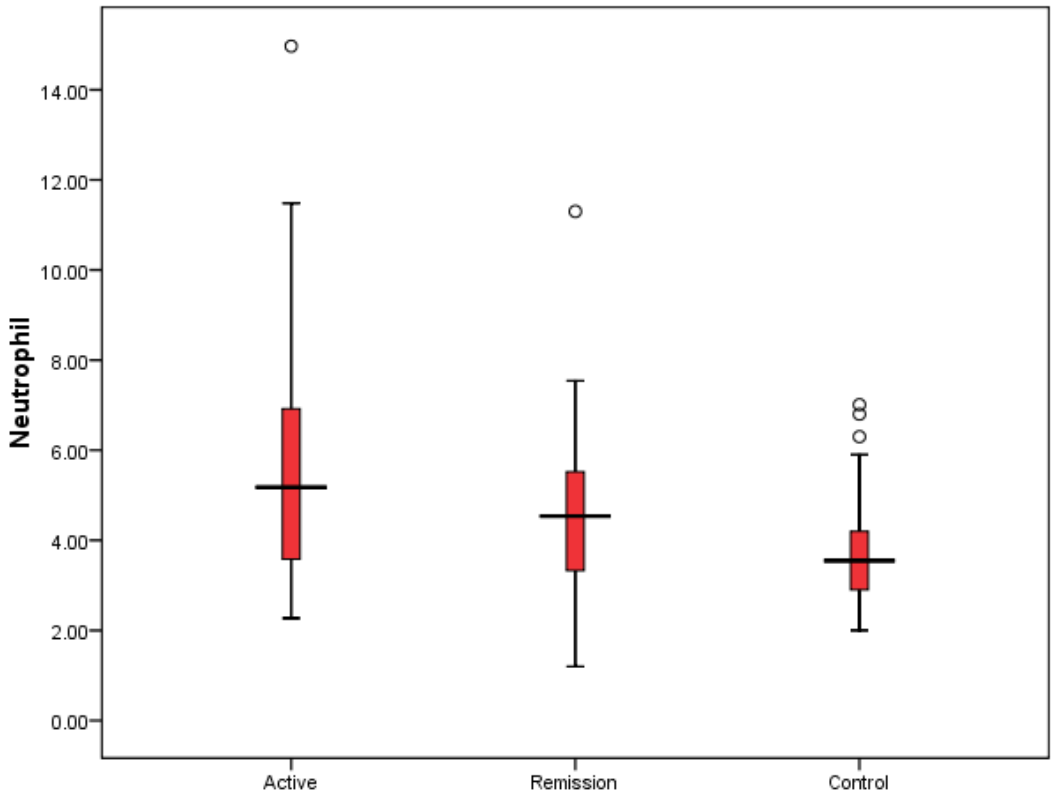

Figure 11: comparison between groups as regard Neutrophil count

Table (4) : Comparison between active group and remission group regarding liver function test results

parameters	**Active n=30 (group I)**	**Remission n=30 (group II)**	**Test of significance**
SGPT	17.0 (10.0-40.0)	18.5 (11.0-70.0)	z=0.386 p=0.7
SGOT	15.0 (1.0-38.0)	22.0 (10.0-48.0)	z=2.01 p=0.053
Serum total Bilirubin	0.6 (0.2-1.2)	0.9 (0.2-1.2)	z=2.53 p=0.06
Serum albumin	2.91±0.59 (1.4-3.7)	3.64±0.39 (2.8-4.6)	t=5.7 p<0.001**

All parameters described as median (min –max) except Serum albumin described as mean ± SD(min-max)

Z:Mann Whitney U test for non parametric variables t: Student t tes for parametric variables

*P: probability * p value significant if <0.05 ** p value high statistically significant <0.01*

Table (4) showed that:

Regarding Liver function tests, SGPT, SGOT and Serum Total Bilirubin in active SLE group (group I) show no significant difference compared to those in remission group (group II), they were (p=0.7, p=0.053, p=0.06 respectively) Serum Albumin level of active SLE group (group I) 2.91±0.59 (1.4-3.7) was significantly decreased compared to remission group (group II) 3.64±0.39(2.8-4.6) p<0.001.

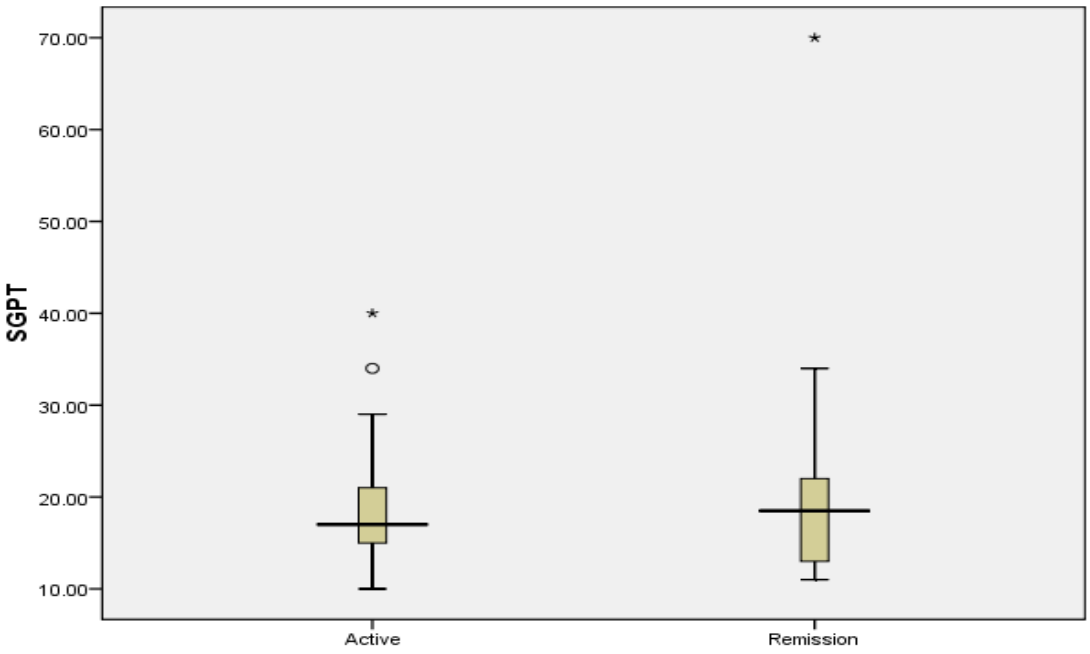

Figure 12: comparison between active and remission groups as regard SGPT

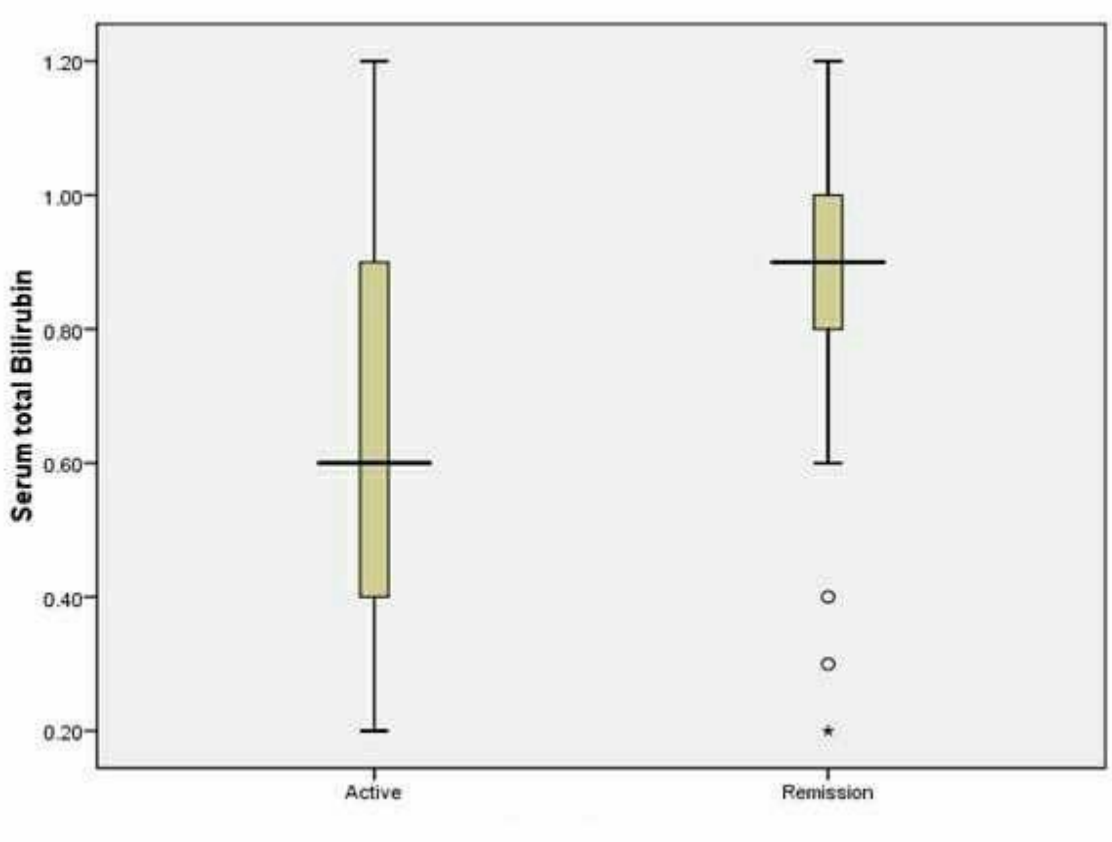

Figure 13: comparison between active and remission groups as regard Serum Bilirubin

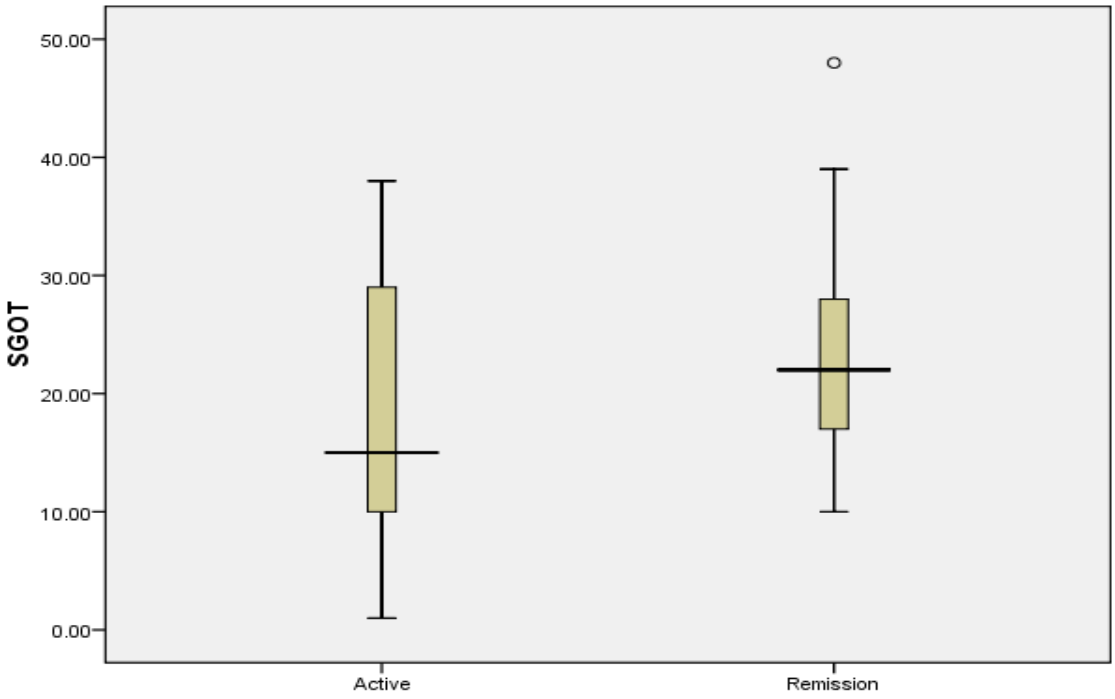

Figure 14: comparison between active and remission groups as regard SGOT

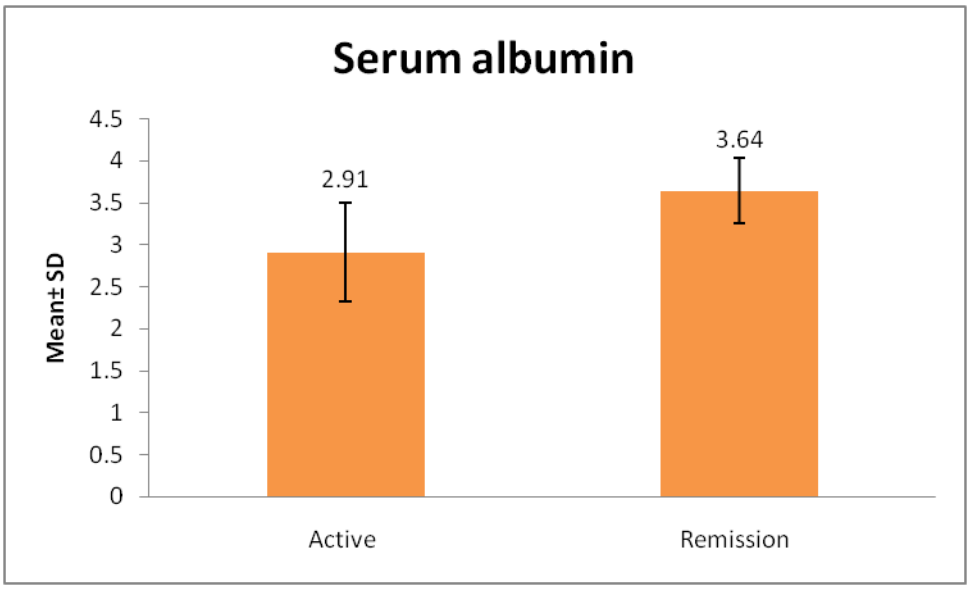

Figure 15: comparison between active and remission groups as regard S. Albumin

Table (5) : Comparison between active group and remission group regarding kidney function test results

parameters	**Active n=30 group I**	**Remission n=30 group II**	**Test of significance**
Serum creatinine	0.95 (0.3-7.1)	0.90 (0.5-3.2)	z=1.18 p=0.24
BUN	20.0 (8.0-209.0)	19.0 (11.0-77.0)	z=0.75 p=0.45

All parameters described as median (min –max) *Z:Mann Whitney U test*

P: probability ** p value significant if <0.05*

Table (5) showed that:

Regarding Kidney function tests, serum creatinine and BUN in active SLE group (group I) show no significant difference compared to those in remission group (group II), they were (p=0.24, p=0.45 respectively)

Table (6) : Comparison between active group and remission group regarding immune markers results

parameters	**Active n=30 (group I)**	**Remission n=30 (group II)**	Test of significance
ANA	n(%)	n(%)	
• negative	0(0.0)	12(40.0)	χ^2=18.38 p<0.001**
• positive	7(23.3)	9(30.0)	
• high positive	23(76.7)	9(30.0)	
ADNA			
• negative	4(13.3)	21(70.0)	χ^2=19.82 p<0.001**
• positive	26(86.7)	9(30.0)	
C3 (mean ±SD)	77.89±14.7	106.27±16.44	t=7.05 p<0.001**
C4 (mean ±SD)	12.44 ± 3.5	24.95 ± 8.82	t=6.29 p<0.001**

t: Student t test for parametric variables *P: probability* ** p value significant if <0.05*

χ^2*=Chi –Square test for categorical variables, to compare between different groups*

*** p value high statistically significant <0.01*

Table (6) showed that:

Regarding ANA titres , values were categorized into :

1-negative (<1/160) 2- positive (1/160-1/960) 3- highly positive (> 1/960) (in some laboratories, this is reported in international units in which 1 IU is equivalent to ANA titre of 1:160) ***(Hugle ., et al 2014)***

Comparison between (group I) and (group II) showed that there was a high statistically significant difference between active SLE (group I) & cases in remission (group II) regarding ANA ($p<0.001$) .

Regarding A.DNA , values were categorized into :

1-negative**:** (< 5 IU/mL) 2- positive : (>5 IU/mL) ***(Fu ., et al 2015)***

Comparison between group I and group II showed that there was a high statistically significant difference between active SLE (group I) & cases in remission (group II) regarding A.DNA ($p<0.001$) .

C3 mean value in active SLE group (group I) (77.89±14.7) ,was significantly decreased compared to remission group (group II) (106.27±16.44) , $p<0.001$

C4 mean value in active SLE group (group I) (12.44 ± 3.5) ,was significantly decreased compared to remission group (group II) (24.95 ± 8.82), $p<0.001$

Table (7) : Comparison between active group and remission group Regarding ESR & CRP results.

parameters	**Active n=30 group I**	**Remission n=30 group II**	**Test of significance**
ESR	74.0 (30.0-150.0)	59.0 (5.0-130.0)	z=1.82 p=0.07
CRP	27.5 (12.0-96.0)	13.5 (7.5-24.0)	z=4.15 p<0.001**

All parameters described as median (min –max) *Z:Mann Whitney U test*

P: probability ** p value significant if <0.05*

Table (7) showed that:

Active SLE group (group I) had higher ESR value but yet not statistically significant compared to those in remission group (group II), they were (p=0.07).

CRP level in active SLE group (group I) 27.5 (12.0-96.0) ,was significantly increased compared to remission group (group II) 13.5 (7.5-24.0), p<0.001

Table (8) : Comparison between active , remission and control groups regarding NLR & PLR results

parameters	**Active n=30 group I**	**Remission n=30 group II**	**Control n=30 group III**	Test of significance
NLR	5.28 (2.71-12.04)	2.44 (1.44-5.4)	1.915 (1.14-3.55)	p1<0.001** p2<0.001** p3=0.076
PLR	320.74 (150.0-751.3)	153.85 (50.17-242.0)	147.62 (96.9-228.0)	p1<0.001** p2<0.001** p3=0.511

Used test: KruskalWallis test and Mann Whitney U test for non parametric values

P1: difference between active SLE and SLE in remission, P2: difference between active SLE and Control group , P3: difference between SLE in remission and Control group

*P: probability * p value significant if <0.05 ** p value high statistically significant <0.01*

Table (8) showed that:

Median NLR of active SLE group (group I), 5.28(2.71-12.04) was significantly increased compared to both, remission group (group II), 2.44(1.44-5.4) , p1<0.001and to control group (group III),1.915 (1.14-3.55), p2<0.001. But there was no statistically significant difference between remission group (group II) and control group (group III) p3=0.076.

Median PLR of active SLE group (group I), 320.74(150.0-751.3) was significantly increased compared to both, remission group (group II), 153.85 (50.17-242.0) , $p1<0.001$ and to control group (group III) ,147.62 (96.9-228.0), $p2<0.001$. But there was no statistically significant difference between remission group (group II) and control group (group III) $p3=0.511$.

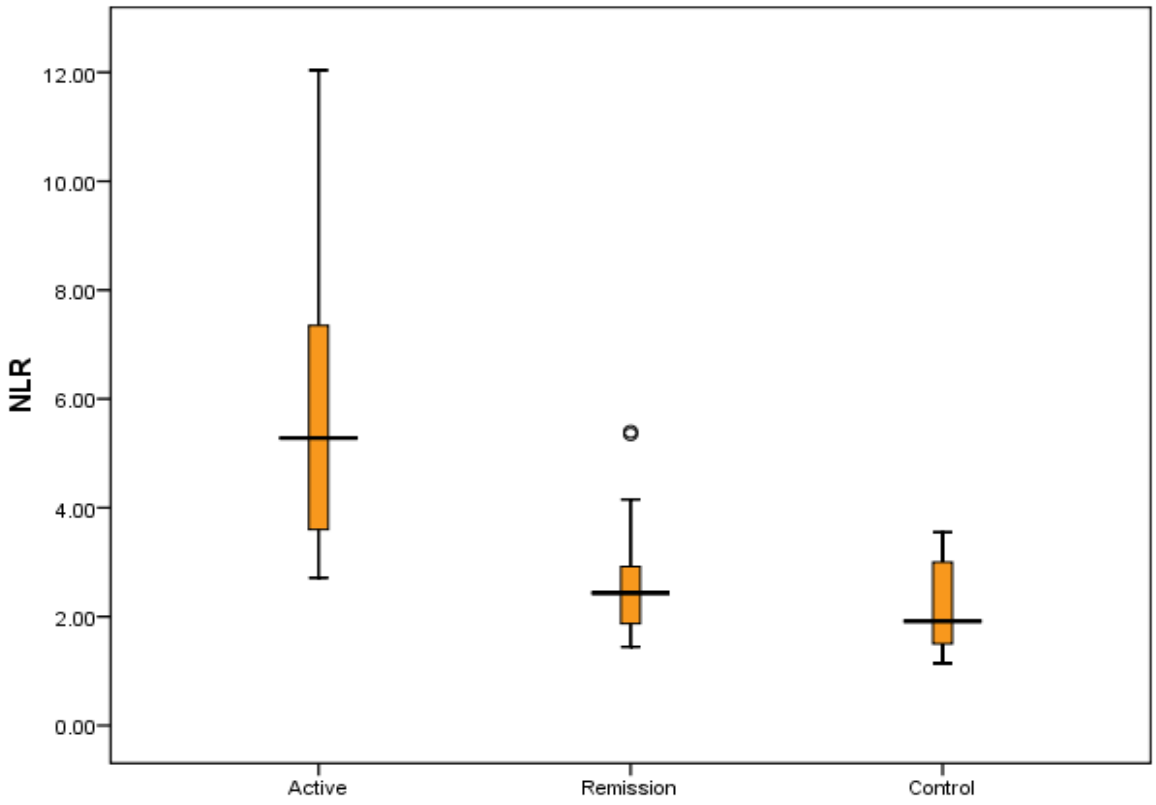

Figure 16: comparison between groups as regard NLR

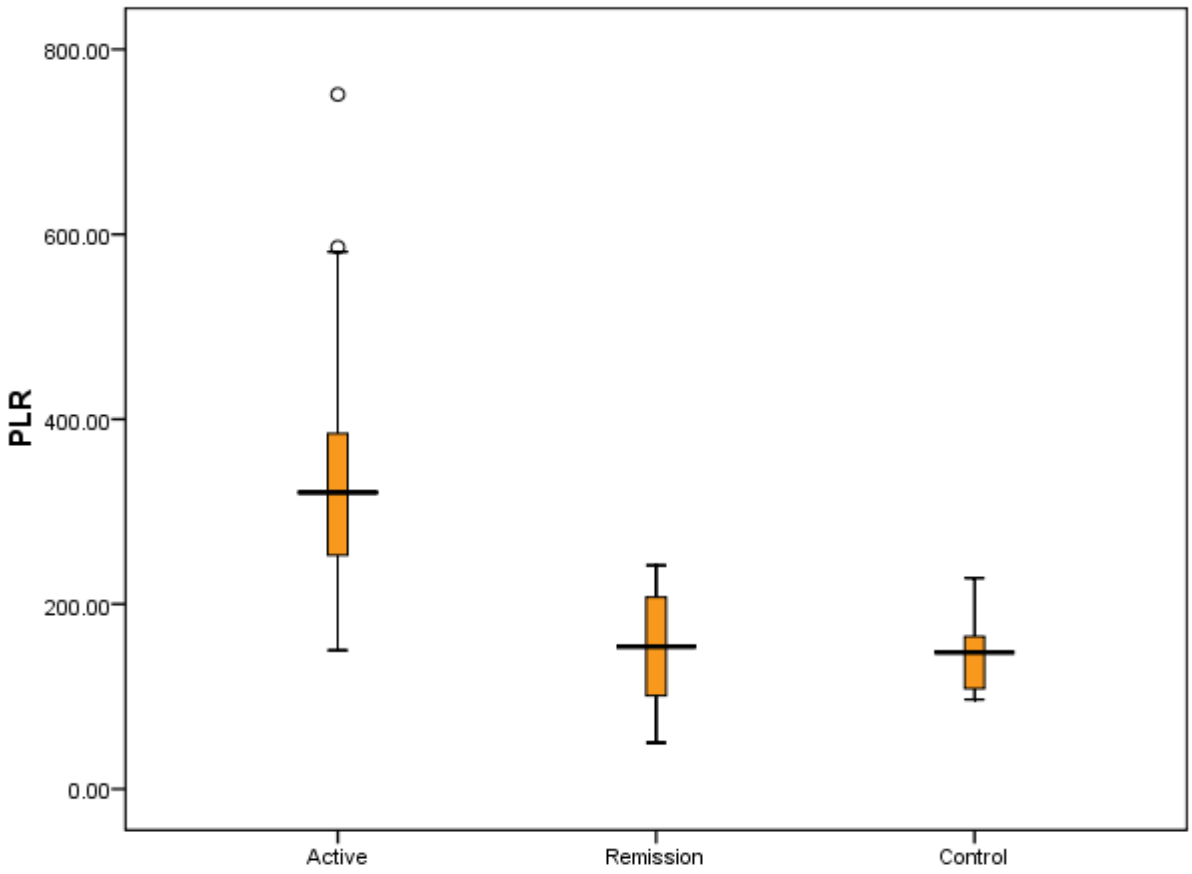

Figure 17: comparison between groups as regard PLR

Table (9) : Binary logistic regression In prediction of SLE active Cases

predictors	β	p	odds ratio (95% CI)
NLR	1.31	<0.001**	3.69(1.86-7.33)
PLR	0.034	0.001**	1.035(1.015-1.055)

β : Constant

P: probability ** p value significant if <0.05* *** p value high statistically significant <0.01*

Table (9) showed that:

NLR &PLR were significant predictors of Active SLE .Every increase in NLR one unit increase risk of activity of SLE by 3.69 times (OR =3.69 ; 95% CI :1.86-7.33) and every increase in PLR one unit increase risk of activity of SLE by 1.035 times (OR =1.035 ; 95% CI :1.015-1.055).

Table (10) : correlation between NLR , PLR and laboratory results in active SLE cases (group I)

parameters	NLR		PLR	
	rs=	p=	rs=	p=
ANA	0.565	0.001**	0.074	0.008**
A.DNA	0.347	0.007**	0.386	0.002**
C3	-0.458	<0.001**	-0.576	<0.001**
C4	-0.62	<0.001**	-0.638	<0.001**
Pr/Creat ratio	0.33	0.07	0.636	0.066
ESR	0.262	0.043*	0.32	0.013*
CRP	0.366	0.015*	0.423	0.004**
Sledai Score	0.589	0.006**	0.509	0.04*

*rs : Spearman correlation coefficient P: probability * p value significant if <0.05*

*** p value high statistically significant <0.01*

Table 10 showed that:

There was a statistically significant strong positive correlation between ANA and NLR (p= .001, rs= 0.565) and a statistically significant strong positive correlation between ANA and PLR (p= .008, rs=0.74).

A statistically significant positive correlation was found between A.DNA and NLR (p=0.007, rs=0 .347) and a statistically significant positive correlation between A.DNA and PLR (p=0.002 , rs= 0.386).

C3 and NLR showed a statistically significant negative correlation (p<0.001, rs= -0 .458). Moreover, there was a statistically significant strong negative correlation between C3 and PLR (p<0.001.rs= -0.576).

There was a statistically significant strong negative correlation between C4 and NLR (p<0.001, rs= -0 .62) and a statistically significant Strong negative correlation between C4 and PLR (p<0.001 , rs= -0.638).

There was no statistically significant correlation between Protein/Creatinine Ratio and NLR and PLR (p= 0.07 and 0.066 respectively)

There was a statistically significant positive correlation between ESR and NLR (p=0.043, rs=0 .262) and a statistically significant positive correlation between ESR and PLR (p=0.013 , rs= 0.32).

A statistically significant positive correlation was confirmed between CRP and NLR (p=0.015, rs=0 .366) and a statistically significant positive correlation between CRP and PLR (p=0.004 , rs= 0.423).

There was a statistically significant strong positive correlation between SLEDAI Score and NLR (p= .006, rs= 0.589) and a statistically significant strong positive correlation between SLEDAI Score and PLR (p= .04, rs= 0.509).

DISCUSSION

Systemic Lupus Erythematosus is a chronic multi-organ autoimmune disease in which the body's immune system mistakenly attacks healthy tissue in many parts of the body. Symptoms vary between people and may be mild to severe. Common symptoms include painful and swollen joints, fever, chest pain, hair loss, mouth ulcers, enlarged lymph nodes, fatigue. ***(Wu et al., 2016)***

The global rates of SLE are approximately 20-70 per 100,000 people. In females,the rate is highest between 16-45 year of age. The lowest overall rate exists in Iceland and Japan. The highest rates exist in US and France .SLE, like many autoimmune diseases, affects females more frequently than males, at a rate of about 9 to 1. ***(Danchenko et al., 2006)***

Assessing disease activity in SLE is crucial to the physician as it forms the basis for treatment decisions. Disease activity needs to be distinguished from damage as this has important implications for the long term prognosis and the appropriate treatment. Several validated global and

organ-specific activity indices are widely used in the evaluation of SLE patients ***(Urowitz and Gladman., 2011).***

The accepted measures of disease activity in SLE include erythrocyte sedimentation rate (ESR), plasma/serum complement component 3 (C3) and component 4 (C4) and presence of antibodies to double-stranded DNA (anti-dsDNA). Some patients, however, have abnormalities in these tests for considerable periods yet show few clinical symptoms or functional deterioration of a major organ; others are markedly symptomatic with only minor aberrations in these test results ***(Rahman and Hiepe ., 2002***).

Most patients with SLE develop kidney disease related to this systemic underlying disease process. Lupus Nephritis is the most common and severe clinical manifestation of SLE. **(*Borchers et al., 2012*)**.

White blood cell (WBC) count is a serum marker for systemic inflammation. Neutrophil-lymphocyte ratio is easily calculated by dividing neutrophil count by the absolute lymphocyte count from a complete blood count. It is simple and cheap. Many studies have shown that NLR is positively associated with inflammatory, different malignancies, ischemic

injury, cardiovascular disease and diabetic nephropathy .***(Ahsen et al., 2013; Li et al., 2014; Maharaj et al., 2015)***

Platelet to lymphocyte ratio (PLR) is an easy calculated parameter. Studies have shown that increased PLR is associated with neoplastic diseases like lung cancer .Moreover PLR is a better predictor than NLR for survival in patients with ovarian cancer.***(Feng et al., 2013)***

So, the present study aimed to evaluate the value of Neutrophil Lymphocyte ratio and Platelet Lymphocyte ratio as simple, rapid and cheap prognostic markers of the activity of Systemic Lupus Disease.

The study recruited 60 patients with SLE, as 30 active cases and 30 in remission. They were subjected to careful history taking, thorough clinical and laboratory investigations including CBC , Liver and Kidney functions and immunological parameters as ANA , Anti-Ds DNA , C3 and C4.

All cases are 60 as 59 female (98.33) and only 1 male (1.67).Active SLE cases are all females 30(100.0). Remission cases are 30 as 29 female (96.7) and 1 male (3.3).Mean age of active SLE group is 28.0±9.04 and mean age of remission group is 27.73±7.6. All cases age ranged from (16-45) with mean age 27.88±8.3.

These Findings were in agreement with ***Ginzler et al., (2015)*** ,who reported that More than 90% of cases of SLE occur in women frequently starting at childbearing age.

As regard results of complete blood picture (CBC), active SLE group (group I) and cases in remission (group II) had no statistically significant difference as regard mean hemoglobin count ,platelet count, neutrophil count and total leucocytic count (p=0.085, p= 0.057, p=0.19 and p= 0.469 respectively). This was against , ***Stojan et al., (2013***) who reported that leukopenia is common and may reflect active disease. Moreover , anemia and thrombocytopenia may also be observed with active disease. This may be due to small number of cases included in our study.

On the other hand, Lymphocyte count level of active SLE group (group I), was significantly decreased compared to remission group (group II) , p1<0.001 and control group (group III).This was in agreement with ***Amaylia et al ., (2013)*** who reported that lymphopenia is a chief finding in Lupus flactuaions and can reflect case activity.

Regarding Liver function tests, SGPT, SGOT and Serum Total Bilirubin in active SLE group (group I) showed no significant difference compared to

those in remission group (group II) , they were (p=0.7, p=0.053, p=0.06 respectively). This was against ***Piga et al ., (2010),*** who reported that fluctuations in the levels of liver function tests corresponding to SLE activity have been reported in some patients with SLE

Meanwhile, Serum Albumin level of active SLE group (group I) 2.91±0.59 (1.4-3.7) was significantly decreased compared to remission group (group II) 3.64±0.39(2.8-4.6) p<0.001. This was in agreement with ***Yip et al ., (2010)*** who reported that serum albumin as a marker for disease activity in patients with systemic lupus erythematosus, with and without nephritis.

Regarding Kidney function tests, serum creatinine and BUN in active SLE group (group I) show no significant difference compared to those in remission group (group II), they were (p=0.24, p=0.45 respectively). On the contrary ***Borchers et al., (2012***) reported that elevated renal function tests is a sign of SLE activity.

Disagreement with ***Borchers et al., (2012***) may be due to relatively few number of confirmed Lupus Nephritis cases in our study as they are only four cases. Moreover ,if we used creatinine clearance and/or protein creatinine ratio in urine in comparison, this might have given us more significant results.

Complement component 3, often simply called C3, is a protein of the immune system. It plays a central role in the complement system and contributes to innate immunity.

Complement component 4 (C4), is a protein involved in the intricate complement system, originating from the human leukocyte antigen (HLA) system. It serves a number of critical functions in immunity, tolerance, and autoimmunity with the other numerous components.

The cause of complement activation in SLE is the formation of immune complexes, which in turn activate complement, predominantly by means of the classical pathway leading to complement depletion. Complement activation is normally measured in clinical practice by estimation of levels of both C3 and C4 (***Birmingham et al., 2010)***

In present study, there was a highly statistical significant decrease in both C3 and C4 found in group I (active SLE) in comparison to group II (Remission) ($p<0.001$ for both).

This was in agreement with, ***Nived et al.,(2004)*** who observed that low complement concentrations and also high activation of the complement system are characteristic findings in active SLE and had led to the practice of using measurement of complement for the diagnosis.

Anti-nuclear antibodies (ANA) are autoantibodies to the nuclei of cells. 98% of all people with systemic lupus have a positive ANA test, making it the most sensitive diagnostic test for confirming diagnosis of the disease.(***Esdaile et al.,2001)***

In our study , ANA titre values were categorized into :

1-negative (<1/160) 2- positive (1/160-1/960) 3- highly positive (> 1/960)

Regarding ANA, there was a high statistically significant increase found in group I (active SLE) in comparison to group II (Remission) ($p<0.001$).

This was in agreement with, ***Jennings et al.,(1997)*** who reported that ANA test is highly sensitive test and that it is positive in more than 98% of people with SLE.

Anti-dsDNA is a protein directed against double-stranded DNA. The test is very specific for lupus. Therefore, a positive test can be useful in confirming a diagnosis. For many people, the titer, or level, of the antibodies rises as the disease becomes more active. So, it can also be used to help measurement of disease activity. Also, the presence of anti-dsDNA indicates a greater risk of lupus nephritis, a kidney inflammation that occurs with lupus. So a positive test can alert doctors to the need to monitor the kidneys.(***Rahman and Hiepe , 2002)***

In the present study ,A.DNA values were categorized into :

1-negative**:** (< 5 IU/mL) 2- positive : (>5 IU/mL)

Regarding A.DNA, there was a high statistically significant increase found in group I (active SLE) in comparison to group II (Remission) ($p<0.001$).

This was in agreement with ***Abd-Elhafeez et al., (2017)*** reported that rising titres of A.DNA can be used to confirm SLE disease activity.

In the current study, there was a statistical significant increase in ESR in group I (active SLE) in comparison to group II (Remission) (p=0.04).

Stoll et al.,(1996) noted that ESR is used as a marker of inflammation. Inflammation could indicate lupus activity. This test could be used to monitor inflammation, which could indicate changes in disease activity or response to treatment.

On the contrary , ***Haq et al.,(2002)*** reported that there are many causes for a positive result, including infection; the test is not diagnostic for lupus, Nor it can distinguish a lupus flare from an infection. Moreover, the level doesn't directly correlate with lupus disease activity. So it is not necessarily useful for monitoring disease activity.

Moreover, ***Jennings et al.,(1997)*** reported that the erythrocyte sedimentation rate is a sensitive but non-specific indicator of activity in SLE and is slow to reflect changes in disease activity.

C-reactive protein (CRP) is an annular (ring-shaped) protein , found in plasma. It is an acute-phase protein of hepatic origin whose levels rise in response to inflammation. (***Thompson et al., 1999).***

Regarding CRP, there was a highly statistically significant increase in CRP in patients of group I (active SLE) in comparison to group II (Remission) ($p<0.001$)

Mok et al.,(2003) reported that CRP is elevated with activity of lupus and positively and significantly correlates with lupus disease activity Index.

The neutrophil-to-lymphocyte ratio (NLR) is a simple ratio of the absolute neutrophil and lymphocyte counts obtained on the differential section of the total white blood cell count (WBC) of a complete blood cell (CBC) count. NLR is a marker of inflammatory response and has been shown to be associated with poor outcomes in patients with several types of diseases. ***(Grivennikov et al ., 2010).***

In addition, ***Chua et al.,(2011)*** observed that Neutrophil Lymphocyte ratio (NLR) has been evaluated and used as inflammatory marker in malignancies, infection and coronary artery diseases.

In the present work, there was a highly statistical significant increase in NLR in patients of group I (active SLE) in comparison to group II (remission group) and group III (control group). Moreover, there was no statistical significant increase in NLR in patients of group II (remission group) in comparison to group III (control group).

On the same side, ***Amaylia et al., (2013)***, found that NLR was significantly higher in SLE than normal subjects. Moreover, ***Lixiu et al., (2015)*** found that high NLR is independently associated with SLE activity, and showed a significant increase in NLR in Lupus nephritis patients. They stated that NLR could reflect inflammatory response and disease activity in SLE patients.

Furthermore, this was in agreement with, ***Yunxiu et al.,(2016)*** who reported that NLR was increased in SLE patients in comparison to control. They also reported that NLR was increased in active group in comparison

to remission group. Meanwhile, ***Delgado et al.,(2015)*** showed that NLR is not superior to lymphocyte alone in differentiating disease activity in SLE.

Platelet Lymphocyte Ratio (PLR) is a novel inflammatory biomarker used as prognostic factor in various diseases such as diabetes mellitus, coronary artery disease, ulcerative colitis and inflammatory arthritis and malignancies ***.(Akkaya et al., 2014)*** .

In the present study, there was high statistical increase in PLR in patients of group I (active SLE) in comparison to group II (Remission) and group III (control group). Moreover, there was no statistical significant increase in PLR in patients of group II (remission group) in comparison to group III (control group).

The SLEDAI is a global index that was developed and introduced in 1985 as a clinical index for the assessment of lupus disease activity in the preceding 10 days. It consists of 24 weighted clinical and laboratory variables of nine organ systems. SLEDAI was modeled on the basis of clinician global judgment. The scores of the descriptors range from 1 to 8, and the total possible score for all 24 descriptors is 105 **.**

Activity categories have been defined on the basis of SLEDAI scores:

1-No activity (SLEDAI =0). 2-Mild activity (SLEDAI =1-5).

3-Moderate activity (SLEDAI = 6-10) 4-High activity (SLEDAI = 11-19).

5- Very high activity (SLEDAI 20).***(Lo and Tsokos , 2011)***

Active SLE cases in our study (30 cases) were classified into:

Mild active (12 cases), moderate active (9 cases), highly active(6 cases) and very highly active (3 cases)

Trying to correlate NLR with other known markers of SLE activity, there was a positive correlation of NLR in patients of group I (active SLE) in relation to (ESR,CRP, ANA, A.DNA and SLEDAI Score). Also there was a strong negative correlation in NLR in patients of in group I (active SLE) in relation to (C3 and C4) .

This was in agreement with, ***Baodong et al.,(2016)*** which observed that NLR was increased in SLE and positivity correlated with other markers of activity.

In addition, there was a positive correlation of PLR in patients of group I (active SLE) in relation to markers of activity (ANA, AdsDNA, ESR and CRP). Furthermore, there was a statistically significant negative correlation found between PLR and (C3 and C4) (P value for both <0.001) .

The present study showed that , PLR was positivity correlated with SLEDAI,(p=0.04).This was in agreement with ***Baodong et al.,(2016)*** which observed that PLR was increased in SLE with lupus nephritis in comparison to SLE without nephritis and positivity correlated with increasing scores of SLEDAI.

Summary

Systemic Lupus Erythematosus is a chronic multi-organ autoimmune disease in which the body's immune system mistakenly attacks healthy tissue in many parts of the body. Symptoms vary between people and may be mild to severe. Common symptoms include painful and swollen joints, fever, chest pain, hair loss, mouth ulcers, enlarged lymph nodes, fatigue ***(Wu et al., 2016)***

The accepted measures of disease activity in SLE include erythrocyte sedimentation rate (ESR) , plasma/serum complement component 3 (C3) and component 4 (C4) and presence of antibodies to double-stranded DNA (anti-dsDNA). Some patients, however, have abnormalities in these tests for considerable periods yet show few clinical symptoms or functional deterioration of a major organ; others are markedly symptomatic with only minor aberrations in these test results ***(Rahman and Hiepe , 2002)***

Neutrophil-lymphocyte ratio is easily calculated by dividing neutrophil count by the absolute lymphocyte count from a complete blood count. It is simple and cheap. Many studies have shown that NLR is positively associated with inflammatory, different malignancies, ischemic injury, cardiovascular disease and diabetic nephropathy ***(Ahsen et al., 2013 ; Li et al., 2014) .***

Platelet to lymphocyte ratio (PLR) is an easy calculated parameter. Studies have shown that increased PLR is associated with neoplastic diseases like lung cancer ***(Feng et al., 2013)***

This study was held to evaluate the value of neutrophil lymphocyte ratio and platelet lymphocyte ratio as simple and cheap prognostic markers of the activity of systemic lupus disease.

This study is a prospective study that is conducted on 60 patients diagnosed with Systemic Lupus Erythematosus in internal medicine department , Ain Shams University Hospitals and 30 control persons. All between 16 and 45 years old taken

from October 2016 till April 2017. Informed written consent were taken from all subjects enrolled in the study.

When comparing NLR between groups, level of active SLE group, 5.28(2.71-12.04) was significantly increased compared to both, remission group, 2.44(1.44-5.4), and control group ,1.915 (1.14-3.55).

As regard PLR, the level of active SLE group, 320.74(150.0-751.3) was significantly increased compared to both, remission group , 153.85 (50.17-242.0) and control group ,147.62 (96.9- 228.0).

Both NLR and PLR were positively correlated with known markers of activity .Our study showed that there was a positive correlation of NLR and PLR in patients of group A (active SLE) in relation to (, ESR,CRP, ANA, A.DNA and SLEDAI Score). Moreover, there was a strong negative correlation in NLR and PLR in (active SLE) in relation to (Lymphocytes , C3 and C4) .

Conclusion

Neutrophil lymphocyte ratio (NLR) and Platelet Lymphocyte ratio (PLR) are simple and cheap prognostic markers of the activity of Systemic Lupus Disease. Both are correlated with well known markers of activity of SLE and can be used to follow up SLE cases and rapidly asses the response to treatment They are cheap, quick and easily measurable; they may be promising marker that reflect activity changes in patients with SLE.

Recommendations

• Other larger studies may help in confirming that NLR and PLR can be used as markers of activity of SLE.

•Other studies are needed to asses NLR and PLR as activity markers in other autoimmune diseases.

• NLR and PLR in SLE patients with other co-morbidities as (HIV , HBV, HCV , chronic renal disease or blood diseases) should be studied to evaluate the effect of variant co-morbidities on SLE patients and asses the result on NLR and PLR levels.

• Further studies may be needed to evaluate NLR and PLR in various malignant diseases and their relation to remission state.

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الملخص العربى

يعتبر مرض الذئبة الحمراء أحد الأمراض المناعية المزمنة و التى تصيب العديد من الأعضاء فى وقت واحد . و فيها يقوم الجسم بمهاجمة نفسه عن طريق الخطأ، وتتباين الأعراض بين المرضى من أعراض بسيطة إلى أعراض شديدة .

من أشهر أعراض هذا المرض تورم و آلام المفاصل و حمى و آلام بالصدر و فقدان للشعر و كذلك ظهور قرح بالفم و تورم بالغدد الليمفاوية و الإحساس بالإعياء الشديد .

هناك العديد من التحاليل المستخدمة لتشخيص مدى نشاط هذا المرض منها تحليل سرعة الترسيب و نسبة الخلايا المتممه ٣ و ٤ و نسبة مضادات حمض الدي أوكسى ريبونيوكليك أسيد و لكن تم إثبات أن هذه التحاليل ليست بالكافية لتأكيد نشاط مرض الذئبة .

تعد نسبة الخلايا المتعادلة إلى الخلايا الليمفاوية وكذلك نسبة الصفائح الدموية إلى الخلايا الليمفاوية مقياسا سهلا و سريعا و قليل التكلفة لتشخيص عديد من الأمراض و الأورام مثل أمراض القلب و الأمراض الروماتيزمية و سرطان الرئة .

هذه الدراسة مستعرضة و تناولت ٦٠ مريضا يعانون من مرض الذئبة و الذين ترددوا على أقسام الباطنة العامة بجامعة عين شمس فى الفترة من أكتوبر ٢٠١٦ حتى إبريل ٢٠١٧، حيث تم تقسيم الحالات لمجموعتين مجموعة أ و هى عبارة عن ٣٠ حالة تعانى من المرض فى مرحلة النشاط و مجموعة ب و هى عبارة عن ٣٠ حالة فى مرحلة التعافى . هذا بالإضافة إلى مجموعة ج و هى عبارة عن ٣٠ شخص سليم .

يجدر الإشارة إلى أنه تم أخذ موافقات كتابية من جميع الأشخاص الذين تمت عليهم الدراسه.

بمقارنة نسبة الخلايا المتعادلة إلى الخلايا الليمفاوية بين المجموعات الثلاث تبين زيادة النسبة فى المجموعة الأولى (المرض النشط) إلى المجموعتين الثانية و الثالثة

و بمقارنة نسبة الصفائح الدموية إلى الخلايا الليمفاوية بين المجموعات الثلاث تبين زيادة النسبة فى المجموعة الأولى (المرض النشط) إلى المجموعتين الثانية و الثالثة ..

و بالربط بين نسبة الخلايا المتعادلة إلى الخلايا الليمفاوية و كذلك الصفائح الدموية إلى الخلايا الليمفاوية بالمقاييس و التحاليل الآخرى المستخدمة عادةً لتشخيص نشاط المرض تبين أن هناك علاقة طردية قوية بينهم .

دراسة النسبة بين الخلايا المتعادلة إلى الخلايا الليمفاوية و النسبة بين الصفائح الدموية إلى الخلايا الليمفاوية كمؤشر و مقياس لمدى نشاط المرض فى حالات الذئبة الحمراء

رساله تمهيديه

مقدمه من

ط / أحمد ممدوح على على

بكالوريوس الطب والجراحة كلية طب المنصورة

مقيم باطنة عامة

توطئة للحصول على درجة الماجستيرفى الباطنة العامة

المشرفـــون

الأستاذة الدكتورة / أمل مصطفى العفيفى

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مدرس الباطنة العامة و أمراض الدم وزرع النخاع

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